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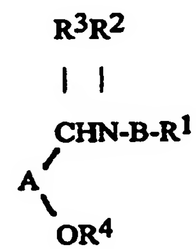
(54) Title: AROMATIC COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

The invention relates to compounds of formula (I), wherein A is an optionally substituted ring system, provided that the $-CH(R^3)N(R^2)B-R^1$ and $-OR^4$ groups are positioned in a 1,2 relationship to one another on ring carbon atoms and the ring atom positioned ortho to the OR^4 linking group (and therefore in the 3-position relative to the $-CHR^3NR^{2-}$ linking group) is not substituted; B is an optionally substituted ring system: R^1 is positioned on ring B in a 1,3 or 1,4 relationship with the $-CH(R^3)N(R^2)-$ linking group and is as defined in the specification. R^2 is hydrogen, C_{1-6}alkyl, optionally substituted by hydroxy, cyano or trifluoromethyl, C_{2-6}alkenyl (provided the double bond is not in the 1-position), C_{2-6}alkynyl (provided the triple bond is not in the 1-position), phenylC_{1-3}alkyl or pyridylC_{1-3}alkyl; R^3 is hydrogen, methyl or ethyl; R^4 is optionally substituted: C_{1-6}alkyl, C_{3-7}cycloalkylC_{1-3}alkyl or C_{3-7}cycloalkyl; and N-oxides of $-NR^2$ where chemically possible; and S-oxides of sulphur containing rings where chemically possible; and pharmaceutically acceptable salts and *in vivo* hydrolysable esters and amides thereof. Processes for their preparation, their use as therapeutic agents and pharmaceutical compositions containing them.



(I)

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Aromatic compounds and pharmaceutical compositions containing them

This invention relates to novel, aromatic compounds and pharmaceutically-acceptable salts thereof which possess useful pharmacological properties. More particularly the compounds of the invention are antagonists of the pain enhancing effects of E-type prostaglandins. The invention also relates to processes for the manufacture of the aromatic compounds and pharmaceutically-acceptable salts thereof; to novel pharmaceutical compositions containing them; and to use of the compounds in pain relief.

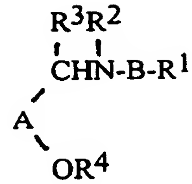
The compounds of the invention are useful in the treatment of pain such as the pain associated with joint conditions (such as rheumatoid arthritis and osteoarthritis), postoperative pain, post-partum pain, the pain associated with dental conditions (such as dental caries and gingivitis), the pain associated with burns (including sunburn), the treatment of bone disorders (such as osteoporosis, hypercalcaemia of malignancy and Paget's disease), the pain associated with sports injuries and sprains and all other painful conditions in which E-type prostaglandins wholly or in part play a pathophysiological role.

Non-steroidal anti-inflammatory drugs (NSAIDS) and opiates are the main classes of drugs in pain relief. However both possess undesireable side effects. NSAIDS are known to cause gastrointestinal irritation and opiates are known to be addictive.

We have now found a class of compounds structurally different to NSAIDS and opiates, and useful in relief of pain.

The compounds of the invention may also possess anti-inflammatory, anti-pyretic and anti-diarrhoeal properties and be effective in other conditions in which prostaglandin E_2 (PGE_2) wholly or in part plays a pathophysiological role.

According to the invention there is provided a compound of the formula I:



(I)

wherein:

A is an optionally substituted:

phenyl, naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidyl, thienyl, thiazolyl, oxazolyl or thiadiazolyl having at least two adjacent ring carbon atoms;

provided that the $-CH(R^3)N(R^2)B-R^1$ and $-OR^4$ groups are positioned in a 1,2 relationship to one another on ring carbon atoms and the ring atom positioned ortho to the OR^4 linking group (and therefore in the 3-position relative to the $-CHR^3NR^2-$ linking group) is not substituted;

B is an optionally substituted:

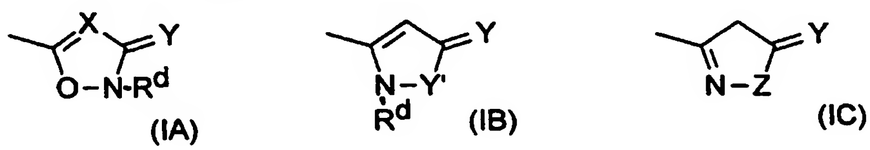
phenyl, pyridyl, thiazolyl, oxazolyl, thienyl, thiadiazolyl, imidazolyl, pyrazinyl, pyridazinyl or pyrimidyl;

R^1 is positioned on ring B in a 1,3 or 1,4 relationship with the $-CH(R^3)N(R^2)-$ linking group and is carboxy, carboxyC_{1-3}alkyl, tetrazolyl, tetrazolylC_{1-3}alkyl, tetronic acid, hydroxamic acid, sulphonic acid, or R^1 is of the formula $-CONR^aR^{a1}$ wherein R^a is hydrogen or C_{1-6}alkyl and R^{a1} is hydrogen, C_{1-6}alkyl (optionally substituted by halo, amino, C_{1-4}alkylamino, di-C_{1-4} alkylamino, hydroxy, nitro, cyano, trifluoromethyl, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl), C_{2-6}alkenyl (provided the double bond in not in the 1-position), C_{2-6}alkynyl (provided the triple bond is not in the 1-position), carboxyphenyl, 5- or 6-membered heterocyclylC_{1-3}alkyl, 5- or 6-membered heteroarylC_{1-3}alkyl, 5- or 6-membered heterocyclyl, or 5- or 6-membered heteroaryl or R^a and R^{a1} together with the amide nitrogen to which they are attached (NR^aR^{a1}) form an amino acid residue or ester thereof, or R^1 is of the formula $-CONHSO_2R^b$ wherein R^b is C_{1-6}alkyl (optionally substituted by halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-4}alkoxy, amino, C_{1-4}alkylamino, di-C_{1-4}alkylamino or C_{1-4}alkoxycarbonyl), C_{2-6}alkenyl (provided the double bond is not in the 1-position), C_{2-6}alkynyl (provided the triple bond is not in the 1-position), 5- or 6-membered heterocyclylC_{1-3}alkyl, 5- or 6-membered

heteroarylC_{1-3}alkyl, phenylC_{1-3}alkyl, 5- or 6-membered heterocyclyl, 5- or 6-membered heteroaryl or phenyl;

wherein any heterocyclyl or heteroaryl group in R^{a1} is optionally substituted by halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl and any phenyl, heterocyclyl or heteroaryl group in R^b is optionally substituted by halo, trifluoromethyl, nitro, hydroxy, amino, cyano, C_{1-6}alkoxy, C_{1-6}alkylS(O)p-(p is 0, 1 or 2), C_{1-6}alkyl carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoylamino, C_{1-4}alkanoyl(N-C_{1-4}alkyl)amino, C_{1-4}alkanesulphonamido, benzenesulphonamido, aminosulphonyl, C_{1-4}alkylaminosulphonyl, di(C_{1-4}alkyl)aminosulphonyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkanoyloxy, C_{1-6}alkanoyl, formylC_{1-4}alkyl, hydroxyiminoC_{1-6}alkyl, C_{1-4}alkoxyiminoC_{1-6}alkyl or C_{1-6}alkylcarbamoylamino; or R^1 is of the formula -SO2N(R^c)R^{c1} wherein R^c is hydrogen or C_{1-4}alkyl and R^{c1} is hydrogen or C_{1-4}alkyl;

or R^1 is of the formula (IA), (IB) or (IC):



(IA) (IB) (IC)

wherein X is CH or nitrogen, Y is oxygen or sulphur, Y' is oxygen or NR^d and Z is CH_2, NR^d or oxygen provided that there is no more than one ring oxygen and there are at least two ring heteroatoms and wherein R^d is hydrogen or C_{1-4}alkyl;

R^2 is hydrogen, C_{1-6}alkyl, optionally substituted by hydroxy, cyano or trifluoromethyl, C_{2-6}alkenyl (provided the double bond is not in the 1-position), C_{2-6}alkynyl (provided the triple bond is not in the 1-position), phenylC_{1-3}alkyl or pyridylC_{1-3}alkyl;

R^3 is hydrogen, methyl or ethyl;

R^4 is optionally substituted: C_{1-6}alkyl, C_{3-7}cycloalkylC_{1-3}alkyl or C_{3-7}cycloalkyl;

and N-oxides of $-NR^2$ where chemically possible;

and S-oxides of sulphur containing rings where chemically possible;

and pharmaceutically acceptable salts and in vivo hydrolysable esters and amides thereof;

excluding 2-[2-methoxybenzylamino]pyridine-5-carboxylic acid, 4-[2-methoxybenzylamino]benzoic acid, 5-[2,3-dimethoxybenzylamino]-2-chloro-3-aminosulphonylbenzoic acid and 5-[2,5-dimethoxybenzylamino]-2-hydroxybenzoic acid

A 5- or 6-membered heteroaryl ring system is a monocyclic aryl ring system having 5 or 6 ring atoms wherein 1, 2 or 3 ring atoms are selected from nitrogen, oxygen and sulphur.

A 5- or 6-membered saturated or partially saturated heterocyclic ring is a ring system having 5 or 6 ring atoms wherein 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen and sulphur.

Particular 5- or 6-membered monocyclic heteroaryl rings include pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiazolyl, thiadiazolyl, thienyl, furyl and oxazolyl.

Particular 5- or 6-membered saturated or partially saturated heterocyclic ring systems include pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl and morpholinyl.

Particular substituents for ring carbon atoms in A (heterocyclyl and heterocryl rings include halo, trifluoromethyl, nitro, hydroxy, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, cyano, C_{1-6}alkoxy, C_{1-6}alkyl$S(O)_p$- (p is 0, 1 or 2), C_{1-6}alkyl (optionally substituted by hydroxy, amino, halo, nitro or cyano), $CF_3S(O)_p$-(p=0,1 or 2), carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoylamino, C_{1-4}alkanoyl(N-C_{1-4}alkyl)amino, C_{1-4}alkanesulphonamido, benzenesulphonamido, aminosulphonyl, C_{1-4}alkylaminosulphonyl, C_{1-4}alkanoylaminosulphonyl, di(C_{1-4}alkyl)aminosulphonyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkanoyloxy, C_{1-6}alkanoyl, formylC_{1-4}alkyl, trifluoroC_{1-3}alkylsulphonyl, hydroxyiminoC_{1-6}alkyl, C_{1-4}alkoxyiminoC_{1-6}alkyl and C_{1-6}alkylcarbamoylamino.

Where a ring nitrogen atom in A can be substituted without becoming quaternised, it is unsubstituted or substituted by C_{1-4}alkyl.

Particular substituents for ring carbon atoms in B include halo, trifluoromethyl, nitro, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino,

cyano. C_{1-6}alkyl S(O)p-(p is 0, 1 or 2), carbamoyl, C_{1-4}alkylcarbamoyl and di(C_{1-4}alkyl)carbamoyl.

Where a ring nitrogen atom in B can be substituted without becoming quaternised, it is unsubstituted or substituted by C_{1-4}alkyl.

The term alkyl when used herein includes straight chain and branched chain substituents for example methyl, ethyl, n-propyl, isopropyl, n-butyl and isobutyl and functional groups on alkyl chains may be anywhere on the chain, for example hydroxyiminoC_{1-6}alkyl includes 1-(hydroxyimino)propyl and 2-(hydroxyimino)propyl.

C_{1-6}alkyl substituted by halo includes trifluoromethyl.

Amino acid residues formed from R^a and R^{a1} together with the nitrogen to which they are attached include residues (-NHCH(R)COOH) derived from naturally-occurring and non-naturally-occurring amino acids. Examples of suitable amino acids include glycine, alanine, serine, threonine, phenylalanine, glutamic acid, tyrosine, lysine and dimethylglycine.

Suitable ring systems of the formula (IA), (IB), or (IC) include 5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl, 3-oxo-2,3-dihydro-1,2,4-oxadiazol-5-yl, 3-thioxo-2,3-dihydro-1,2,4-oxadiazol-5-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, 5-oxo-4,5-dihydro-1,2,4-triazol-3-yl, 5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, 1,3,4-oxadiazol-2-yl, 3-hydroxy-2-methylpyrazol-5-yl, 3-oxo-2,3-dihydroisoxazol-5-yl, 5-oxo-1,5-dihydroisoxazol-3-yl and 5-oxo-2,3-dihydropyrazol-3-yl.

Examples of C_{1-6}alkoxycarbonyl are methoxycarbonyl, ethoxycarbonyl and t-butoxycarbonyl; examples of carboxyC_{1-3}alkyl are carboxymethyl, 2-carboxyethyl, 1-carboxyethyl and 3-carboxypropyl; examples of C_{1-6}alkoxycarbonylC_{1-3}alkyl are methoxycarbonylmethyl, ethoxycarbonylmethyl and methoxycarbonylethyl; examples of tetrazolylC_{1-3}alkyl are tetrazolylmethyl and 2-tetrazolylethyl; examples of C_{1-4}alkoxy are methoxy, ethoxy, propoxy and isopropoxy; examples of C_{2-6}alkenyl are vinyl and allyl; examples of C_{2-6}alkynyl are ethynyl and propynyl; examples of C_{1-4}alkanoyl are formyl, acetyl, propionyl and butyryl; examples of halo are fluoro, chloro, bromo and iodo; examples of C_{1-4}alkylamino are methylamino, ethylamino, propylamino and isopropylamino; examples of di(C_{1-4}alkyl)amii are dimethylamino, diethylamino and ethylmethylamino; examples of C_{1-6}alkylS(O)$_p$- are methylthio, methylsulphinyl and

methylsulphonyl; examples of C_{1-4}alkylcarbamoyl are methylcarbamoyl and ethylcarbamoyl; examples of di(C_{1-4}alkyl)carbamoyl are dimethylcarbamoyl, diethylcarbamoyl and ethylmethylcarbamoyl; examples of C_{1-6}alkyl are methyl, ethyl, propyl and isopropyl; examples of C_{1-4}alkoxycarbonylamino are methoxycarbonylamino and ethoxycarbonylamino; examples of C_{1-4}alkanoylamino are acetamido and propionamido; examples of C_{1-4}alkanoyl(N-C_{1-4}alkyl)amino are N-methylacetamido and N-methylpropionamido; examples of C_{1-4}alkanesulphonamido are methanesulphonamido and ethanesulphonamido; examples of C_{1-4}alkylaminosulphonyl are methylaminosulphonyl and ethylaminosulphonyl; examples of di(C_{1-4}alkyl)aminosulphonyl are dimethylaminosulphonyl, diethylaminosulphonyl and ethylmethylaminosulphonyl; examples of C_{1-4}alkanoyloxy are acetyloxy and propionyloxy; examples of formylC_{1-4}alkyl are formylmethyl and 2-formylethyl; examples of hydroxyiminoC_{1-6}alkyl are hydroxyiminomethyl and 2-(hydroxyimino)ethyl; and examples of C_{1-4}alkoxyiminoC_{1-6}alkyl are methoxyiminomethyl, ethoxyiminomethyl and 2-(methoxyimino)ethyl.

It will be understood that when formula I compounds contain a chiral centre, the compounds of the invention may exist in, and be isolated in, optically active or racemic form. The invention includes any optically active or racemic form of a compound of formula I which possesses pain-relieving properties. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by, resolution of a racemic form, by synthesis from optically active starting materials or by asymmetric synthesis. It will also be appreciated that certain compounds of formula I may exist as geometrical isomers. The invention includes any geometrical isomer of a compound of formula I which possesses pain-relieving properties.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of relieving pain.

It will further be understood that the present invention encompasses tautomers of the compounds of the formula (I).

Preferably A is optionally substituted:

phenyl. naphthyl. thiadiazolyl. thienyl, pyridyl or pyrimidyl.

Preferably B is optionally substituted:

pyridyl, phenyl. thiazolyl, thienyl, pyridazinyl. or oxazolyl.

Most preferably A is optionally substituted:

phenyl or thienyl.

Most preferably B is optionally substituted:

pyridyl. phenyl. thienyl. pyridazinyl or thiazolyl.

In particular A is optionally substituted phenyl.

In particular B is optionally substituted:

pyrid-2.5-diyl, pyridazin-3.6-diyl, phen-1,4-diyl or thien-2,5-diyl.

Most particularly B is optionally substituted pyridazin-3.6-diyl or pyrid-2,5-diyl.

Most preferably B is pyridazinyl.

Preferred optional substituents for ring carbon atoms in A. are halo. nitro. trifluoromethyl, cyano, amino. C_{1-6}alkoxy. carbamoyl. C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl. C_{1-4}alkanoylamino, C_{1-6}alkylS(O)$_p$-, C_{1-4}alkanesulphonamido, benzenesulphonamido, C_{1-6}alkanoyl. C_{1-4}alkoxyiminoC_{1-4}alkyl and hydroxyiminoC_{1-4}alkyl.

Preferably, when A is a 6-membered ring, A is unsubstituted or substituted in the 4-position relative to the -OR^4 group.

Preferred optional substituents for ring carbon atoms of B are halo. trifluoromethyl, C_{1-4}alkyl, amino, C_{1-4} alkylamino. diC_{1-4} alkylamino, nitro, hydroxy, C_{1-6}alkoxy and cyano.

Preferably A is unsubstituted or substituted by one substituent.

More preferably A is unsubstituted or substituted by bromo, methanesulphonyl, fluoro or chloro.

Most preferably A is unsubstituted or substituted by bromo or chloro.

Preferably B is unsubstituted or substituted by one substituent.

Most preferably B is unsubstituted.

Preferably R^1 is carboxy, carbamoyl or tetrazolyl or R^1 is of the formula -CONR^{a}R^{a1} wherein R^a is hydrogen or C_{1-6}alkyl and R^{a1} is C_{1-6}alkyl optionally substituted by hydroxy, C_{2-6}alkenyl, 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl,

pyridylC_{1-3}alkyl or R^1 is of the formula $-CONHSO_2R^b$ wherein R^b is optionally substituted:

C_{1-6}alkyl, phenyl or 5- or 6-membered heteroaryl.

In particular, R^1 is carboxy, tetrazolyl or of the formula $-CONR^a R^{a1}$ wherein R^a is hydrogen and R^{a1} is C_{1-6}alkyl optionally substituted by hydroxy or pyridylmethyl, or R^1 is of the formula $-CONHSO_2R^b$ wherein R^b is C_{1-6}alkyl (optionally substituted by hydroxy or fluoro), phenyl (optionally substituted by acetamido), isoxazolyl (optionally substituted by methyl) or 1,3,4-thiadiazolyl (optionally substituted by acetamido).

Most preferably R^1 is carboxy, tetrazole or of the formula $-CONHR^{a1}$ wherein R^{a1} is pyridylmethyl or C_{1-4}alkyl optionally substituted by hydroxy, or of the formula $-CONHSO_2R^b$ wherein R^b is C_{1-4} alkyl, 3,5-dimethylisoxazol-4-yl, or 5-acetamido-1,3,4-thiadiazol-2-yl.

In another aspect R^1 is carboxy, carbamoyl or tetrazolyl or R^1 is of the formula $-CONR^a R^{a1}$ wherein R^a is hydrogen or C_{1-6}alkyl and R^{a1} is C_{1-6}alkyl optionally substituted by hydroxy, C_{2-6}alkenyl, 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl, pyridylC_{1-3}alkyl or R^1 is of the formula $-CONHSO_2R^b$ wherein R^b is C_{1-6}alkyl or phenyl.

Preferably R^2 is hydrogen, methyl, ethyl, 2,2,2-trifluoroethyl, cyanomethyl, allyl or 3-propynyl.

More preferably R^2 is hydrogen, methyl, ethyl or propyl.

Yet more preferably R^2 is hydrogen or ethyl.

Most preferably R^2 is ethyl.

Preferably R^3 is hydrogen.

Preferably R^4 is optionally substituted by halo, hydroxy, C_{1-4}alkoxy, amino, carboxy, C_{1-4} alkylS(O)p-(p=0, 1 or 2), carbamoyl, trifluoromethyl, oxo or cyano.

More preferably R^4 is optionally substituted by fluoro, chloro or bromo.

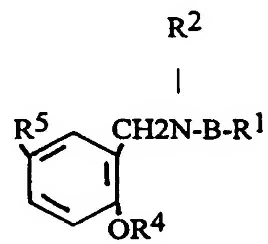
Most preferably R^4 is optionally substituted by fluoro, trifluoromethyl, cyano or hydroxy.

Preferably R^4 is C_{1-4}alkyl, C_{3-6}cycloalkyl or C_{3-6}cycloalkylmethyl.

More preferably R^4 is propyl, isobutyl, butyl, 2-ethylbutyl, 2(R)-methylbutyl, 2(S)-methylbutyl, 2,2,2-trifluoroethyl, cyclopent: methyl, cyclopropylmethyl, cyclopropyl or cyclopentyl.

Most preferably R^4 is propyl, isobutyl, butyl, 2-ethylbutyl, cyclopentyl, cyclopropylmethyl or cyclopropyl.

A preferred class of compounds is that of the formula (II):



(II)

wherein

R^1 and R^2 are as hereinabove defined, R^4 is C_{1-4}alkyl, C_{3-6}cycloalkyl or C_{3-6} cycloalkylmethyl, R^5 is hydrogen or as hereinabove defined for substituents for ring carbon atoms in A, and B is phenyl, thienyl, pyridazinyl, pyridyl, or thiazolyl.

It is to be understood that, insofar as certain of the compounds of formula (I) defined above may exist in optically active or racemic forms, by virtue of the compounds of the formula (I) containing an asymmetric carbon atom, the invention includes in its definition of active ingredient any such optically active or racemic form which possesses pain relieving properties. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, pain relieving properties may be evaluated using the standard laboratory techniques referred to hereinafter.

An <u>in vivo</u> hydrolysable ester of a compound of the formula (I) containing carboxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid, for example, a pharmaceutically acceptable ester formed with a (1-6C)alcohol such as methanol, ethanol, ethylene glycol, propanol or butanol, or with a phenol or benzyl alcohol such as phenol or benzyl alcohol or a substituted phenol or benzyl alcohol wherein the substituent is, for example, a halo (such as fluoro or chloro), (1-4C)alkyl (such as methyl) or (1-4C)alkoxy (such as ethoxy) group.

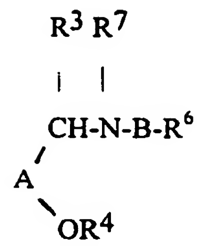
The term also includes α-acyloxyalkyl esters and related compounds which breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl esters include acetoxymethoxycarbonyl and 2,2-dimethylpropionyloxymethoxycarbonyl.

An in vivo hydrolysable ester of a compound of the formula (I) containing a hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent alcohol. The term includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the in vivo hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of in vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable value for an in vivo hydrolysable amide of a compound of the formula I containing a carboxy group is, for example, a N-(1-6C)alkyl or N,N-di-(1-6C)alkyl amide such as N-methyl, N-ethyl, N-propyl, N,N-dimethyl, N-ethyl-N-methyl or N,N-diethyl amide.

A suitable pharmaceutically-acceptable salt of a compound of the formula (I) is, for example, an acid-addition salt of a compound of the formula (I) which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of the formula (I) which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

In a further aspect the invention provides a process for preparing compounds of the formula (I) or pharmaceutically acceptable salts or in vivo hydrolysable amides or esters thereof, which comprises deprotecting a compound of the formula (III):



(III)

wherein R^6 is R^1 or protected R^1, R^7 is R^2 or protected R^2 and, R^3, R^4, A and B are as hereinabove defined, and any optional substituents are optionally protected and at least one protecting group is present;

and thereafter if necessary:

i) forming a pharmaceutically acceptable salt;

ii) forming an <u>in vivo</u> hydrolysable ester or amide;

iii) converting one optional substituent into another optional substituent.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question, and may be introduced by conventional methods.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

A suitable protecting group for a hydroxy group is, for example, an arylmethyl group (especially benzyl), a tri-(1-4C)alkylsilyl group (especially trimethylsilyl or tert-butyldimethylsilyl), an aryldi-(1-4C)alkylsilyl group (especially dimethylphenylsilyl), a diaryl-(1-4C)alkylsilyl group (especially tert-butyldiphenylsilyl), a (1-4C)alkyl group (especially methyl), a (2-4C)alkenyl group (especially allyl), a (1-4C)alkoxymethyl group (especially methoxymethyl) or a tetrahydropyranyl group (especially tetrahydropyran-2-yl). The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-charcoal. Alternatively a trialkylsilyl or an aryldialkylsilyl

group such as a tert-butyldimethylsilyl or a dimethylphenylsilyl group may be removed, for example, by treatment with a suitable acid such as hydrochloric, sulphuric, phosphoric or trifluoroacetic acid, or with an alkali metal or ammonium fluoride such as sodium fluoride or, preferably, tetrabutylammonium fluoride. Alternatively an alkyl group may be removed, for example, by treatment with an alkali metal (1-4C)alkylsulphide such as sodium thioethoxide or, for example, by treatment with an alkali metal diarylphosphide such as lithium diphenylphosphide or, for example, by treatment with a boron or aluminium trihalide such as boron tribromide. Alternatively a (1-4C)alkoxymethyl group or tetrahydropyranyl group may be removed, for example, by treatment with a suitable acid such as hydrochloric or trifluoroacetic acid.

Alternatively a suitable protecting group for a hydroxy group is, for example, an acyl group, for example a (2-4C)alkanoyl group (especially acetyl) or an aroyl group (especially benzoyl). The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide.

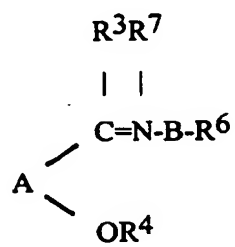
A suitable protecting group for an amino, imino or alkylamino group is, for example, an acyl group, for example a (2-4C)alkanoyl group (especially acetyl), a (1-4C)alkoxycarbonyl group (especially methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl), an arylmethoxycarbonyl group (especially benzyloxycarbonyl) or an aroyl group (especially benzoyl). The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl, alkoxycarbonyl or aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a tert-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid such as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid, and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-charcoal.

A suitable protecting group for a carbo. / group is, for example, an esterifying group, for example a (1-4C)alkyl group (especially methyl or ethyl) which may be

removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide; or, for example, a tert-butyl group which may be removed, for example, by treatment with a suitable acid such as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid.

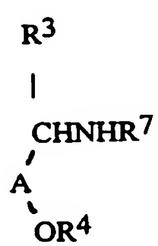
In another aspect the compounds of the formula (I) or (III) may be prepared by:

a) reducing a compound of the formula (IV)



(IV)

b) when B is an activated heterocycle and R^7 is hydrogen or C_{1-6}alkyl reacting a compound of the formula (V) with a compound of the formula (VI):

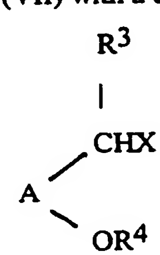


(V)

$X\text{-}B\text{-}R^6$ (VI)

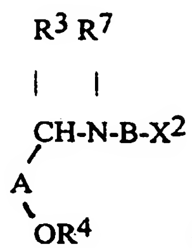
c) reacting a compound of the formula (VII) with a compound of the formula (VIII):

$R^7HN\text{-}B\text{-}R^6$ (VII)



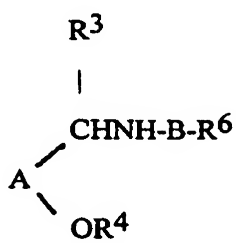
(VIII)

d) converting X^2 to R^6 in a compound of the formula (IX):



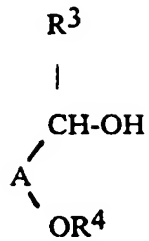
(IX)

e) when R^7 is other than hydrogen, reacting a compound of the formula R^7X^3 with a compound of the formula (X):



(X)

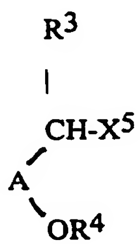
f) reacting a compound of the formula (XI) with a comound of the formula (XII):



(XI)

$X^4NH\text{-}B\text{-}R^6$ (XII)

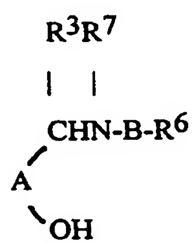
g) reacting a compound of the formula (XIII) with a compound of the formula (XIV):



(XIII)

$X^6NH\text{-}B\text{-}R^6$ (XIV)

h) reacting a compound of the formula (XV) with a compound of the formula X^7R^4:



(XV)

wherein R^3, R^4, R^7, R^9, A and B are as hereinabove defined and X and X^1 are leaving groups, X^2 is a precursor of R^7, X^3 is a leaving group, X^4 is a removable activating group, X^5 is a leaving group, X^6 is an activating group and X^7 is a leaving group; and thereafter if necessary;

i) removing any protecting groups;

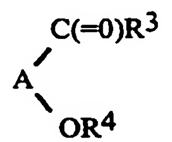
ii) forming a pharmaceutically acceptable salt;

iii) forming an in vivo hydrolysable ester or amide:

iv) converting an optional substituent into another optional substituent.

Particular values for leaving groups include halogen, for example, chloro, bromo and iodo, sulphonates, for example tosylate, p-bromobenzenesulphonate, p-nitrobenzenesulphonate, methanesulphonate and triflate or phosphoric esters such as diarylphosphoric ester.

Compounds of the formula (IV) can be reduced using agents such as sodium borohydride or sodium cyanoborohydride. The compounds of the formula (IV) may be prepared by reacting a compound of the formula (VII) with a compound of the formula (XV)



(XV)

wherein A, R^3 and R^4 are as hereinabove defined.

The reaction between compounds of the formulae (VII) and (XV) may be carried out under standard conditions known in the art for the formation an imine (Schiffs base), which can be reduced in situ. For example imine formation and reduction in situ may be carried out in an inert solvent such toluene or tetrahydrofuran, in the presence of a reducing agent such as sodium cyanoborohydride ($NaCNBH_3$) under acidic conditions (Synthesis 135, 1975; Org. Prep. Proceed. Int. 11, 201, 1979).

Compounds of the formulae (V) and (VI) may be reacted together under standard conditions for example, in an aprotic solvent such as DMF in the presence of a weak base, in a temperature range of ambient to 180°C. Suitable values for X include, halo, tosylate, mesylate and triflate. In particular X is chloro or bromo.

The compounds of the formulae (VII) and (VIII) may be reacted together under in an aprotic solvent such as DMF, in the presence of a base such as potassium carbonate or

sodium hydride and in a temperature range of 0°C to 100°C. Suitable values for X^1 include halo, tosylate, mesylate and triflate. In particular X^1 is bromo.

A precursor of R^7 is a group that can be converted into R^7.

Particular values for X^2 include cyano, carbamoyl, alkoxycarbonyl, carboxy and activated carboxy groups such as acid chlorides and activated esters.

The cyano group may be converted into a tetrazole ring by reacting, for example, with ammonium or tin azide in an aprotic solvent such as DMF, in a temperature range of 100°C to 130°C. For further information on tetrazole synthesis see S.J. Wittenberger and B.J Donner JOC, 1993, 58, 4139-4141; BE Huff et al, Tet. Lett, 1993, 50, 8011-8014; and J.V. Duncia et al, JOC 1991, 56, 2395-2400.

Alkoxycarbonyl may be converted into a carboxy group by acid or base hydrolysis. For example, base hydrolysis may be carried out in an organic solvent such as methanol or THF in a temperature range of ambient to 100°C, in the presence of sodium hydroxide or potassium hydroxide.

Acid hydrolysis may, for example, be carried out in neat formic acid or neat trifluoroacetic acid optionally in an inert organic solvent such as dichloromethane.

An alkoxycarbonyl or an activated carboxy group, such as an acid chloride or activated ester, or an acyl group such as an alkanoyl group may be converted to an amide group by reacting with the appropriate amine in an inert solvent such as DMF or dichloromethane, in a temperature range of 0°C to 150°C, preferably around ambient temperature, in the presence of a base such as triethylamine.

The compounds of the formulae (X) and R^7X^3 may be reacted together in an aprotic solvent such as DMF in the presence of a base such as sodium carbonate or sodium hydride. Suitable values for X^3 are halo, tosylate, mesylate and triflate, in particular halo such as iodo.

The reaction between compounds of the formulae (XI) and (XII) is conveniently carried out under mild conditions known for the Mitsunobu reaction, for example in the presence of di (C_{1-4}alkyl)azocarboxylate and triphenylphosphine or 1^1,1^1-(azodicarbonyl)dipiperidine and tributylphosphine (Tet. Lett. 34, 1993, 1639-1642) in an inert solvent such as toluene, benzene, tetrahydrofuran or diethylether, in particular

toluene. Examples of removable activating groups are tert-butyloxycarbonyl and trifluoroacetyl.

Compounds of the formulae (XIII) and (XIV) are generally reacted together in the presence of a strong base such as sodium hydride, lithium diisopropylamine or LiN(SiMe3)2, in DMF or an etherial solvent such as ethyl ether or THF in a temperature range of -78°C to ambient temperature. Suitable values for X^5 are halogen, for example, methanesulphonate or tosylate. Examples of activating groups for X^6 include tert-butyloxycarbonyl, halogen and trifluoroacetyl.

The reaction between compounds of the formulae (XV) and X^7R^4 may be performed in an inert organic solvent such as acetone or DMF, in a temperature range of ambient temperature to 60°C, in the present of a mild base. Suitable leaving groups include tosylate, mesylate, triflate and halo, for example chloro or bromo. When X^7 is bromo, (XV) and X^7R^4 may be reacted together for example, in DMF, at ambient temperature in the presence of a base such as potassium carbonate. Alternatively a phase transfer systen could be used. X^7 can be hydroxy which is activated in situ using the Mitsunobu reaction (O. Synthesis, 1981, 1.).

Compounds of the formula (XV) wherein R^6 is R^1 and R^7 is R^2 have pain-relieving properties in their own right.

Compounds of the formula (IV), (V), (VIII), (IX), (X), (XI), (XIII) and (XV) can be preapred using processes for the formation of the lower linking group -OR^4, similar to process h), from appropriate starting materials.

The compounds of the formula (IX) may be prepared using processes a), b), c), e), f), g) or h) from the appropriate starting material wherein R^6 is replaced with X^2.

The compounds of the formula (X) may be prepared by using any one of processes a), b), c), d), f), g) or h) from the appropriate starting materials wherein R^7 is hydrogen.

The compounds of the formula (XII) can readily be prepared from compounds of the formula (VII).

The compounds of the formulae (VI), (VII), (XII) and (XIV) are generally known in the art or can be made by methods analogous to or similar to those used in the examples or those known in the art for related compounds. Certain compounds of the formula (VI),

wherein X is chloro or bromo. can be prepared by converting an oxo group in the ring system into chloro or bromo by reacting the oxo ring system with a chlorinating agent, such as sulphonyl chloride, phosphorous trichloride. phosphorous pentachloride or $P(O)Cl_3$ or bromonating agent such as phosphorous tribromide or $P(O)Br_3$. in an inert aprotic solvent.

It is also possible to synthesise certain intermediates and even protected compounds using primarly ring synthesis. Here. reference is made to the compendium 'The Chemistry of Heterocyclic Compounds' E.C. Taylor and A. Weissberger (published by John Wiley and Sons) and 'Comprehensive Heterocyclic Chemistry', A.R Katritsky and C. W Rees (published by Pergamon Press).

Optional substituents may be converted into other optional substituents. For example an alkylthio group may be oxidised to an alkylsulphinyl or alkysulphonyl group, a nitro group reduced to an amino group, a hydroxy group alkylated to a methoxy group, or a bromo group converted to an alkylthio group.

Various substituents may be introduced into compounds of the formulae (I) and (III) and intermediates in the preparation of compounds of the formulae (I) and (III), when appropriate, using standard methods known in the art. For example. an acyl group or alkyl group may be introduced into an activated benzene ring using Friedel-Crafts reactions, a formyl group by formylation with titanium tetrachloride and dichloromethyl ethyl ether, a nitro group by nitration with concentrated nitric acid concentrated sulphuric acid and bromination with bromine or tetra(n-butyl)ammonium tribromide.

It will be appreciated that, in certain steps in the reaction sequence to compounds of the formula (I), it will be necessary to protect certain functional groups in intermediates in order to prevent side reactions. Deprotection may be carried out at a convenient stage in the reaction sequence once protection is no longer required.

As stated hereinbefore compounds of the formula (I) are antagonists of the pain enhancing effects of E-type prostaglandins and of value in the relief of mild to moderate pain which, for example, accompanies inflammatory conditions such as rheumatoid arthritis and osteoarthritis. Certain properties of the compounds may be demonstrated using the test procedures set out below:-

(a) an in-vitro guinea pig ileum assay which assesses the inhibitory properties of a test compound against PGE_2-induced contractions of the ileum: ileum was immersed in oxygenated Krebs solution containing indomethacin (4 μg/ml) and atropine (1 μM) and which was maintained at 37°C: the ileum was subject to a tension of 1 g: a control dose response curve for PGE_2-induced contraction of the ileum was obtained: test compound (dissolved in dimethylsulphoxide) was added to the Krebs solution and a dose response curve for the PGE_2-induced contraction of the ileum in the presence of the test compound was obtained: the pA_2 value for the test compound was calculated;

(b) an in-vivo assay in mice which assesses the inhibitory properties of a test compound against abdominal constriction response induced by the intraperitoneal administration of a noxious agent such as dilute acetic acid or phenylbenzoquinone (hereinafter PBQ) using the procedure disclosed in European Patent Application No. 0218077.

Although the pharmacological properties of the compounds of the formula I vary with structural change as expected, in general activity possessed by compounds of the formula I may be demonstrated at the following concentrations or doses in one or more of the above-mentioned Tests (a) and (b):-

Test (a):- $pA_2 > 5.3$;

Test (b):- ED_{30} in the range, for example, 0.01-100 mg/kg orally.

No overt toxicity or other untoward effects were noted in Test (b) when compounds of the formula I are administered at several multiples of their minimum inhibitory dose.

Prostaglandin receptors and in particular receptors for PGE_2 have been tentatively characterised by Kennedy et al. (Advances in Prostaglandin, Thromboxane and Leukotriene Research, 1983, **11**, 327). The known PGE_2 antagonist SC-19220 blocks the effect of PGE_2 on some tissues such as guinea pig ileum or dog fundus but not on other tissues such as the cat trachea or chick ileum. Those tissues which did possess SC-19220 sensitive mediated effects were said to possess EP_1 receptors. Based on this compounds of the present invention, possessing activity in Test (a), are EP_1 antagonists.

According to a further feature of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I) or an in-vivo hydrolysable ester thereof or an amide thereof. or a pharmaceutically-acceptable salt thereof. in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral use. for example a tablet, capsule. aqueous or oily solution. suspension or emulsion; for topical use. for example a cream. ointment, gel. spray or aqueous or oily solution or suspension; for nasal use, for example a snuff. nasal spray or nasal drops; for vaginal or rectal use, for example a suppository or rectal spray: for administration by inhalation, for example as a finely divided powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous. subcutaneous, intramuscular, intravascular or infusion). for example a sterile aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of active ingredient (that is a compound of the formula (I) or a pharmaceutically-acceptable salt thereof) that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

According to a further feature of the invention there is provided a compound of the formula (1) or an in-vivo hydrolysable ester or amide or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the animal (including human) body by therapy.

According to a further feature of the invention there is provided the use of a compound of the formula I, or an in-vivo hydrolysable ester or amide or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for use in the relief of pain in the animal (including human) body.

According to a further feature of the invention there is provided a method for the relief of pain in the animal (including human) body in need of such treatment which

comprises administering to said body an effective amount of a compound of the formula I, or an in-vivo hydrolysable ester or amide or a pharmaceutically-acceptable salt thereof.

As mentioned above. a compound of the formula (I) is useful in treating the pain which. for example. accompanies inflammatory conditions such as rheumatoid arthritis and osteoarthritis. In using a compound of the formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range. for example. 0.1 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus. for example, for intravenous administration, a dose in the range. for example, 0.05 mg to 30 mg per kg body weight will generally be used. Similarly. for administration by inhalation, a dose in the range, for example. 0.05 mg to 25 mg per kg body weight will be used.

Although the compounds of the formula (I) are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to antagonise the effects of PGE_2 at the EP_1 receptor, based on test a). Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

By virtue of their ability to relieve pain, the compounds of the formula I are of value in the treatment of certain inflammatory and non-inflammatory diseases which are currently treated with a cyclooxygenase-inhibitory non-steroidal anti-inflammatory drug (NSAID) such as indomethacin, ketorolac, acetylsalicyclic acid, ibuprofen, sulindac, tolmetin and piroxicam. Co-administration of a compound of the formula I with a NSAID can result in a reduction of the quantity of the latter agent needed to produce a therapeutic effect. Thereby the likelihood of adverse side-effects from the NSAID such as gastrointestinal effects are reduced. Thus according to a further feature of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or an in-vivo hydrolysable ester or amide or pharmaceutically-acceptable salt thereof, in conjunction or admixture with a cyclooxygenase inhibitory non-steroidal anti-inflammatory agent, and a pharmaceutically-acceptable diluent or carrier.

The compounds of the invention may also be used with other anti-inflammatory agents such as an inhibitor of the enzyme 5-lipoxygenase (such as those disclosed in

European Patent Applications Nos. 0351194, 0375368, 0375404, 0375452, 037547, 0381375, 0385662, 0385663, 0385679, 0385680).

The compounds of the formula (I) may also be used in the treatment of conditions such as rheumatoid arthritis in combination with antiarthritic agents such as gold, methotrexate, steroids and penicillinamine, and in conditions such as osteoarthritis in combination with steroids.

The compounds of the present invention may also be administered in degradative diseases, for example osteoarthritis, with chondroprotective, anti-degradative and/or reparative agents such as Diacerhein, hyaluronic acid formulations such as Hyalan, Rumalon, Arteparon and glucosamine salts such as Antril.

The compositions of the invention may in addition contain one or more other therapeutic or prophylactic agents known to be of value for the treatment of pain. Thus for example, a known opiate pain-killer (such as dextropropoxyphene, dehydrocodeine or codeine) or an antagonist of other pain or inflammation mediators, such as bradykinin, takykinin and calcitonin gene related peptides (CGRP), or an alpha$_2$-adrenoceptor agonist, a GABA$_B$ receptor agonist, a calcium channel blocker, a sodium channel blocker, a CCK$_B$ receptor antagonist, a neurokinin antagonist or an antagonist and modulator of the action of glutamamte at the NMDA receptor may usefully also be present in a pharmaceutical composition of the invention.

The compounds of the present invention may also be adminstered in bone diseases such as osteoporosis with calcitonin and bisphosphonates.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporations <u>in vacuo</u> and work-up procedures were carried out after removal or residual solids by filtration;

(ii) yields are given for illustration only and are not necessarily the maximum attainable;

(iii) the end-products of the formula I have satisfactory microanalysis and their structures were generally confirmed by NMR and mass spectral techniques;

(iv) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the formula I were determined after recrystallisation from a conventional organic solvent such as ethanol. methanol. acetone. ether or hexane. alone or in admixture:

(v) the following abbreviations have been used:-

DMF N.N-dimethylformamide:

THF tetrahydrofuran

DMSO dimethylsulphoxide

TLC thin layer chromatography

MPLC medium pressure liquid chromatography

Example 1

2-[N-(5-Bromo-2-propoxybenzyl)-N-ethylamino]pyridine-5-carboxylic acid

A solution of methyl 2-[N-(5-bromo-2-propoxybenzyl)-N-ethylamino]pyridine-5-carboxylate (reference example 1) (0.12 g, 0.29 mmol) in THF (3 ml) and methanol (3 ml) was treated with aqueous sodium hydroxide (1N, 1.8 ml). The reaction was heated to 40°C for 18 hours. The solvent was then evaporated off and the residue diluted with water (3 ml) and acidified with acetic acid (1N, 3 ml). The solid was filtered off to give the title compound (0.1 g, 88%) as a white solid.

MS (CI+): 393/395 $(M+H)^+$

NMR (200 MHz, DMSO-d6) δ: 1.0 (t, J=7Hz, 3H); 1.12 (t, J=7Hz, 3H); 1.75 (m, 2H); 3.6 (q, J=7Hz, 2H); 3.98 (t, J=7Hz, 2H); 4.73 (s, 2H); 6.65 (d, J=9Hz, 1H); 7.02 (m, 2H); 7.4 (dd, J=2, 9Hz, 1H); 7.92 (dd. J=2,9Hz, 1H); 8.6 (d, J=2Hz, 1H).

Example 2

2-[N-(5-Bromo-2-(2-methyl)propoxybenzyl)-N-ethylamino]-5-pyridinecarboxylic acid

The title compound was prepared using a similar method to that of example 1 except using the appropriate ester (reference example 2).

MS (CI+): 407 $(M+H)^+$

NMR (250 MHz, DMSO-d_6) δ: 1.0 (d, J=6Hz, 6H); 1.05 (t, J=7Hz, 3H), 2.02 (m, 1H); 3.59 (q, J=7Hz, 2H): 3.8 (d, J=6Hz, 2H): 4.75 (s, 2H): 6.64 (d, J=9Hz, 1H). 6.96 (d, J=9Hz, 1H): 7.05 (d, J=2Hz, 1H): 7.36 (dd, J=2.9 Hz, 1H); 7.9 (dd, J=2.9 Hz, 1H); 8.61 (d, J=2Hz, 1H): 12.35 (bs, 1H).

__Example 3__

__6-[N-(5-Bromo-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylic acid__

The title compound was prepared using a similar method to that of example 1 except using the appropriate butyl ester (reference example 4).

mp 73-80°C

MS (FAB+): 406 $(M+H)^+$

NMR (200 MHz, DMSO-d_6 + HOAc-d4) δ 0.15 (m, 2H); 0.38 (m, 2H); 1.02 (m, 4H); 3.55 (q, J = 7Hz, 2H); 3.7 (d, J = 7Hz, 2H); 4.68 (s, 2H); 6.78 (m, 1H); 7.0 (m, 2H); 7.22 (d, J = 9Hz, 1H); 7.5 (d, J = 9Hz, 1H).

__Example 4__

__2-[N-(5-Bromo-2-(cyclopentylmethoxy)benzyl)-N-ethylamino]pyridine-5-carboxylic acid__

A solution of methyl 2-[N-(5-bromo-2-(cyclopentylmethoxy)benzyl)-N-ethylamino]pyridine-5-carboxylate (see reference example 5) (0.37 g, 0.83 mmol) in THF (4 ml) and methanol (4 ml) was treated with 1N aqueous sodium hydroxide solution (4 ml). The reaction was heated at 40°C for 18 hours. The solvents were evaporated at reduced pressure and the residue was acidified with 1N acetic acid (4 ml) and allowed to stir for 2 days. The precipitate was filtered, washed with water and dried in vacuo at 45°C to give the title compound as a white solid (0.32 g, 89%).

MS (ESP+): 433 (M+H)$^-$

NMR (200 MHz. DMSO-d_6) δ: 1.2 (t, J = 7Hz. 3H); 1.35 (m, 2H); 1.58 (m. 4H): 1.75 (m. 2H); 2.30 (m, 1H): 3.60 (q, J = 7Hz. 2H): 3.9 (d, J = 7Hz. 2H); 4.74 (s, 2H); 6.65 (d, J = 9Hz. 1H), 6.98 (d. J = 9Hz. 1H); 7.10 (d. J = 2Hz. 1H): 7.88 (dd. J = 2. 9Hz. 1H); 7.92 (d = 2. 9Hz. 1H): 8.62 (d. J = 2Hz. 1H); 12.4 (vbs. approx. 1H).

Example 5

6-[N-(5-Bromo-2-propoxybenzyl)-N-ethylamino]pyridazine-3-carboxylic acid

The title compound was prepared from butyl 6-[N-(5-bromo-2-propoxybenzyl)-N- ethylamino]pyridazine-3-carboxylate (reference example 6) using a similar method to that of example 1.

MS (ESP$^+$): 394/396 (M+H)$^+$

NMR (200 MHz, DMSO-d_6) δ: 0.97 (t, J = 6.7Hz, 3H); 1.16 (t, J = 6.7Hz, 3H); 1.73 (m, J = 6.7Hz, 2H); 3.7 (q, J = 6.7Hz, 2H); 3.98 (t, J = 6.7Hz, 2H); 4.82 (s, 2H). 7.0 (d, J = 9.3Hz, 1H); 7.12 (d, J = 9.3Hz, 1H); 7.17 (d, J = 2.0Hz. 1H); 7.40 (dd, J = 2.0, 10.0Hz, 1H); 7.83 (d, J = 10.0Hz. 1H).

Example 6

6-[N-(5-Bromo-2-n-butoxybenzyl)-N-ethylamino]pyridazine-3-carboxylic acid

The title compound was prepared from butyl 6-[N-(5-bromo-2-n-butoxybenzyl)-N-ethylamino]pyridazine-3-carboxylate (reference example 7) using a similar method to that of example 1.

MS (ESP$^+$): 408/410 (M+H)$^+$

NMR (200MHz, DMSO-d_6) δ: 0.9 (t, J = 6.7Hz, 3H); 1.14 (t, J = 6.7Hz, 3H); 1.40 (m, J = 6.7Hz, 2H); 1.67 (m, J = 6.7Hz, 2H); 3.67 (q = 6.7Hz, 2H); 4.00 (t, J = 6.7Hz, 2H); 4.8 (s, 2H); 7.0 (d, J = 8.3, 1H); 7.11 (d, J = 10.0Hz. 1H); 7.15 (d, J = 1.7Hz, 1H); 7.40 (dd,

J = 1.7. 8.3Hz. 1H): 7.84 (d. J = 10.0Hz. 1H).

Example 7

N-(3,5-Dimethylisoxazol-4-ylsulphonyl)-6-[N-(5-bromo-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]pyridazine-3-carboxamide

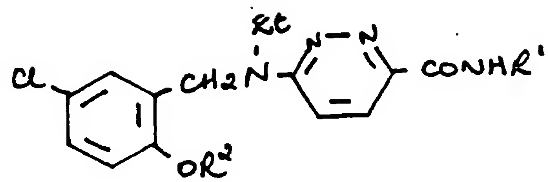
A solution of 6-[N-(5-bromo-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]-pyridazine-3-carboxylic acid (example 3) (0.166 g, 0.409 mmol) in DMF (4 ml) was treated with 3,5-dimethyl-4-sulfonamidoisoxazole (0.08 g, 0.455 mmol), dimethylaminopyridine (0.15 g, 1.23 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride (0.12 g, 0.627 mmol). The reaction was stirred at ambient temperature overnight. TLC (10% $MeOH/CH_2Cl_2$ + 1% HOAc) revealed the reaction had not gone to completion. Further portions of dimethylaminopyridine (0.05 g. 0.409 mmol) and 1-(3-dimethylaminopropyl)-3- ethylcarbodiimidehydrochloride (0.08 g, 0.418 mmol) were added and the reaction stirred at ambient temperature for 60 hours. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by chromatography (eluant: methanol/dichloromethane/acetic acid) to give the title compound as a foam (0.073 g).

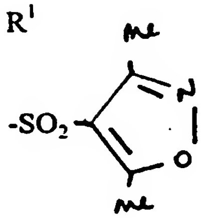
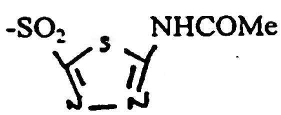
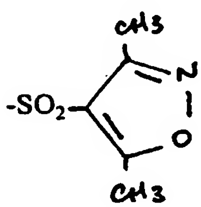
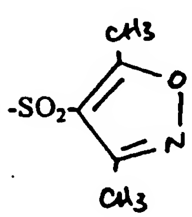
MS (ESP+): 564 $(M+H)^+$

NMR (200 MHz, DMSO-d_6) δ: 0.3 (m, 2H); 0.53 (m, 2H); 1.55 (m, 4H); 2.40 (s, 3H); 2.70 (s, 3H); 3.70 (q, J = 7Hz, 2H); 3.87 (d, J = 7Hz, 2H); 4.85 (s, 2H); 6.98 (d, J = 9Hz, 1H); 7.22 (d, J = 2Hz, 1H); 7.24 (d, J = 9Hz, 1H); 7.39 (dd, J = 2, 9Hz, 1H); 7.83 (d, J = 9Hz, 1H).

Example 8

The compounds in the following table were prepared using a similar method to that of Example 7 from the appropriate carboxylic acid and the appropriate sulphonamide compound.



R[1]	R^2	MS $ES^+ (MH)^+$	Footnote
	$-CH_2CH(Me)CH_3$	522	a
	" "	568	b
$-SO_2CH_2CH_2CH_3$	" "	469	c
	cyclopentyl	534/536	d
$-SO_2CF_3$	"	507/509	e
$-SO_2CH_2CH_2CH_3$	cyclobutylmethyl	480	f
	cyclobutylmethyl	534	g

Footnotes

a) NMR (200MHz. DMSO-d_6)δ: 0.97 (d, 6H); 1.15 (t, 3H); 2.02 (m. 1H); 2.40 (s. 3H); 2.69 (s, 3H); 3.70 (q. 2H); 3.80 (d. 2H); 4.85 (s, 2H); 7.03 (m, 2H); 7.20 (d. 1H); 7.27 (dd. 1H); 7.82 (d, 1H).

Elemental Analysis: $C_{23}H_{28}ClN_5O_5S$ + 0.13 mole toluene

	Theory (%)	Found (%)
C	53.8	53.4
H	5.5	5.5
N	13.1	12.7

b) NMR (200MHz. DMSO-d_6) δ : 0.95 (d, 6H); 1.14 (t, 3H); 2.00 (m. 1H); 2.23 (s, 3H); 3.67 (q, 2H); 3.80 (d, 2H); 4.83 (s, 2H); 7.04 (d,) J=8Hz, 1H); 7.14 (d, J=3Hz, 1H); 7.28 (dd, J=8, 3Hz, 1H); 7.57 (d, J = 9Hz, 1H); 8.05 (d, J=9Hz, 1H); 12.84 (S, 1H).

Elemental Analysis: $C_{22}H_{26}ClN_7O_sS_2$ + 0.1 mole CH_2Cl_2 + 0.2 mole H_2O.

	Theory (%)	Found (%)
C	45.8	45.4
H	4.6	4.5
N	16.9	16.8

m.p. 240-242°C.

c) NMR (200MHz, DMSO-d_6) δ: 1.00 (m, 9H), 1.15 (t, 3H); 1.75 (m, 2H); 2.03 (m, 1H); 3.45 (t, 2H); 3.70 (q, 2H); 3.81 (d, 2H); 4.86 (s, 2H); 7.03 (m, 2H); 7.20 (d, 1H); 7.27 (dd, 1H); 7.87 d, 1H).

Elemental Analysis: $C_{21}H_{29}ClN_4O_4S$

	Theory (%)	Found (%)
C	53.8	53.9
H	6.2	6.2
N	11.9	11.9

d) M.S. (ESP+): 534/536 (MH+)

NMR (200MHz. DMSO-d_6 δ: 1.13(t, 3H): 1.65(br. m): 1.88(br m, 2H): 2.38(s, 3H); 2.68(s. 3H); 3.65(q, 2H); 4.76 (s. 2H); 4.85(m. 1H): 7.00(d. 1H); 7.03(d, 1H): 7.18(d, 1H); 7.24(dd. 1H); 7.82(d. 1H);.

e) M.S. (ESP+): 507/509 (MH+).

NMR (200MHz. DMSO-d_6) δ: 1.11 (t. 3H): 1.60 (br m. 6H); 1.88 (m, 2H): 3.63 (q, 2H); 4.75 (s, 2H); 4.85 (m, 1H); 7.02(d, 1H): 7.30 (m. 2H); 7.88 (d, 2H); 8.20 (d, 2H).

f) M.p.111-113°C

NMR (MHz, DMSO-d_6) δ: 0.92(t, 3H); 1.1(t, 3H); 1.5-2.2 (m, 8H); 2.65(m, 1H); 3.25(m, 2H); 3.68 (q, 2H): 3.95 (d, 2H); 4.8 (s, 2H); 7.0(m, 2H); 7.15(d, 1H); 7.25(dd, 1H); 7.82 (d, 1H).

Elemental Analysis: $C_{22}H_{29}ClSN_4O_4 \cdot 0.75H_2O$

	Theory (%)	Found (%)
C	53.4	53.3
H	6.2	5.8
N	11.3	11.4

g) M.p.140-142°C

NMR (MHz, DMSO-d_6) δ: 1.1(t, 3H); 1.75-2.2 (m, 6H); 2.25(s, 3H); 2.55(s, 3H); 2.70(m, 1H); 3.65 (q, 2H); 4.0 (d, 2H); 4.75 (s, 2H); 7.0(m, 3H); 7.25(dd, 1H); 7.8 (d, 1H).

Elemental Analysis: $C_{24}H_{28S}ClN_5O_5 \cdot H_2O$

	Theory (%)	Found (%)
C	52.2	51.8
H	65.4	5.0
N	12.7	12.5

Example 9

6-[N-(5-Bromo-2-(2-methylpropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylic acid

Butyl 6-[N-(5-bromo-2-(2-methylpropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylate (reference example 10) (0.22g, 0.47mmol) in THF (3ml) and methanol (3ml) was treated with a 1N solution of aqueous sodium hydroxide (3ml) and left at ambient temperature for 1.5 hours (after which time TLC (1:1 diethyl ether/hexane) indicated that none of the ester remained). The reaction mixture was evaporated to low bulk, taken up in a little water and acidified with acetic acid to produce a gum. The gum did not solidify so it was extracted with ethyl acetale (x2) and the combined extracts washed with brine, dried ($MgSO_4$) and evaporated to give a gum. The gum was evaporated from toluene and dichloromethane to give the title compound as a foam (140mg, 73%).

MS (CI^+) : 408.410 $(M+H)^+$

MS (EI^+) : 408.410 $(M+H)^+$

NMR (200MH$_Z$, DMSO-d_6) δ:1.00(d, J= 10Hz, 6H); 1.16(t, J=8.3Hz, 3H); 1.93-2.15 (m, 1H); 3.69(q, J=8.3Hz, 2H); 3.80(d, J=6.67Hz, 2H); 4.84 (s, 2H); 6.98 (d, J=10Hz, 1H); 7.12 (m,2H); 7.40 (dd, J=2, 8.3Hz, 1H); 7.84 (d, J=10Hz, 1H)

Example 10

6-[N-(5-Chloro-2-(2-methylpropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylic acid

The title compound was prepared by hydrolysing butyl 6-[N-(5-chloro-2-(2-methylpropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylate (reference example 12) using a similar method to that of example 1.

NMR (250 MHz. DMSO-d_6) δ: 1.00 (d. 6H): 1.15 (t. 3H); 2.04 (m. 1H): 3.69 (q, 2H); 3.80 (d. 2H): 4.84 (s. 2H): 7.03 (m. 2H): 7.11 (d. 1H): 7.27 (dd. 1H): 7.83 (d. 1H).

MS (ES$^-$) : 362 (M-H)$^-$

Elemental Analysis: $C_{18}H_{22}ClN_3O_3$

	Theory (%)	Found (%)
C	59.4	59.4
H	6.1	5.9
N	11.5	11.4

m.p. 132-134°C.

MS (CI+): 181 (M+H)$^+$

Example 11

6-[N-(5-Bromo-2-(cyclopropylmethoxy)benzyl)-N-ethyl]pyridazine-3-carboxamide

N-Ethyl-5-bromo-2-(cyclopropylmethoxy)benzylamine (reference example 13) (12.56g) was dissolved in NMP (59ml) under argon. 6-Chloropyridazine-3-carboxamide (6.17g, 3.9mmol) and sodium bicarbonate (8.24g, 98mmol) were added and the mixture heated to 110°C for 24 hours. The mixture was then cooled and diluted with ethyl acetate and poured into a mixture of saturated aqueous ammonium chloride and 1N hydrochloric acid (50ml). The white precipitate that formed was filtered off and washed with ethyl acetate and diethyl ether to give the title compound which was dried in a vaccuum oven at 55°C (11.46g, 72.1%).

NMR (200 MHz, DMSO-d_6) δ: 0.34, (m, 2H); 0.55 (m, 2H); 1.17 (m, 4H); 3.69 (q, 2H); 3.88 (d, 2H); 4.80 (s, 2H); 6.96 (d, 1H); 7.15 (m, 2H); 7.37 (dd, 1H); 7.42 (brs, 1H); 7.84 (d, 1H); 8.14 (brs, 1H).

MS (ESP+): 405 (M+H)⁻

Example 12

5-[6-(N-[5-Bromo-2-(cyclopropylmethoxy)benzyl]-N-ethylamino)pyridazin-3-yl]tetrazole

6-[N-(5-Bromo-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]-3-cyanopyridazine (reference example 14) (1.63g) was dissolved in dimethylacetamide (DMA) (17mls) under argon. Triethylamine hydrochlorde (0.87g, 6.3mmol) and sodium azide (0.82g, 12.6mmol) were added and the mixture heated at 95-110°C for 3 hours. It was then cooled and partitioned between saturated aqueous ammonium chloride and ethyl acetate. The organic layer was washed with 10% 2N HCl saturated aqueous ammonium chloride (x2) and brine (x2), dried over Na_2SO_4, filtered and evaporated. The residue was recrystallised from acetonitrile to give the title product (1.34g, 74.0%).

NMR (200MHz, $DMSO_6$) δ : 0.34 (m, 2H); 0.56 (m, 2H); 1.20 (m, 4H); 3.74 (q, 2H); 3.88 (d, 2H); 4.84 (s, 2H); 6.96 (d, 1H); 7.25 (d, 1H); 7.29 (d, 1H); 7.37 (dd, 1H); 8.03 (d, 1H).

Elemental Analysis: $C_{18}H_{20}BrN_7O$

	Theory (%)	Found (%)
C	50.2	50.2
H	4.7	4.8
N	22.8	22.8

MS (ESP^+) : 430 M+H)$^+$

Example 13

5-(6-[N-(5-Chloro-2-(2-methylpropoxy)benzyl)-N-ethylamino]pyridazin-3-)tetrazole

The title compound was prepared from 6-[N-(5-chloro-2-(2-methylpropoxy)benzyl)-N-ethylamino]-3-cyanopyridazine (reference example 15) using a similar method to that of example 12.

NMR (200MHz. DMSO-d_6) δ: 0.99 (d. 6H): 1.18 (t. 3H): 2.04 (m. 1H): 3.72 (q. 2H); 3.82 (d. 2H); 4.86 (s. 2H): 7.04 (d. 1H): 7.09 (d. 1H); 7.27 (m, 2H): 8.03 (d. 1H).

Elemental Analysis: $C_{18}H_{22}ClN_7O$

	Theory (%)	Found (%)
C	55.7	55.6
H	5.7	5.7
N	25.3	24.9

MS (ES$^+$): 388 $(M+H)^+$

m.p. 204-206°C.

Example 14

N-Propanesulphonyl-6-[N-(5-bromo-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]pyridazine-3-carboxamide

6-[N-(5-Bromo-2-(cyclopropylmethoxy)benzyl)-N-ethylamine]pyridazine-3-carboxylic acid (example 3) (1.0g, 2.46mmol) was mixed with propylsulphonamide (0.32g, 2.6mmol), 4-(dimethylamino)pyridine (0.90g, 7.38mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarboxiimide hydrochloride (0.71g, 3.7mmol) under argon. DMF (12.0ml) was added and the mixture stirred at ambient temperature overnight.

The reaction mixture was then poured into saturated aqueous ammonium chloride and extracted with ethyl acetate (x2). The combined organic extracts were washed with 5% 2N HCl in saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate (x1) and brine (x1), dried over Na_2SO_4 filtered and evaporated. The residue was purified by MPLC using 2.5% IPA/dichloromethane + 0.2% acetic acid. Fractions containing the title product were evaporated and the residue codistilled with toluene, isohexane and finally ether so that the title product was obtained as a white foam on drying under high vacuum. (1.00g, 79.4%).

NMR (200 MHz, DMSO-d_6) δ: 0.30, (m. 2H); 0.55 (m, 2H); 1.00 (t, 3H); 1.16 (m, 4H); 1.75 (m, 2H); 3.45 (t, 3H); 3.73 (q, 2H); 3.87 (d, J=7.5Hz. 2H): 4.85 (s. 2H); 6.97 (d,

J=8.3Hz. 1H): 7.18 (d. J=3.1Hz. 1H). 7.24 (d. J=8.7 Hz. 1H): 7.39 (dd. J-8.3. 3.1 Hz. 1H): 7.86 (d, J=8.7Hz. 1H).

Elemental Analysis: $C_{21}H_{27}BrN_4O_4S$

	Theory (%)	Found (%)
C	49.3	49.7
H	5.3	5.6
N	11.0	10.7

Example 15

6-[N-(5-Bromo-2-(2-hydroxy-3,3,3-trifluoropropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylic acid

The title compound was prepared from the n-butyl ester (reference example 16) using a similar method to that of example 1.

NMR: (250 Mhz, DMSOd) δ: 1.15 (t, 3H); 3.68 (g, zH); 4.20 (m, 2H); 4.44 (m, 1H); 4.89 (s, 2H); 7.08 (m, 3H), 7.4 (dd, 1H), 87.83 (d, 1H).

MS: 463 $(M+H)^+$

Example 16

5-[6-(N-[2-(Cyclopropylmethoxy)-5-methanesulphonylbenzyl]-N-ethylamino)pyridazin-3-yl]tetrazole

The title compound was prepared from the appropriate cyano compound (reference example 17) using a similar method to that of example 12 except the mixture was heated at 85°C for approximately 20 hours, monitoring the reaction by TLC. (80% yield).

NMR (200MHz, DMSO-d_6) δ : 0.36 (m, 2H); 0.57 (m, 2H); 1.14-1.35 (m, 4H); 3.08 (s, 3H); 3.78 (q, 2H); 4.03 (d, J=6.2Hz, 2H); 4.93 (s, 2H); 7.25 (d, J=8.3Hz, 1H); 7.35 (d, J=8.3Hz: 1H); 7.68 (d, J=2.1Hz, 1H); 7.83 (dd, J=2.1, 8.3Hz, 1H); 8.05 (d. J=8.3Hz, 1H).

MS (ESP^+): 430 $(M+H)^+$

Example 17

5-[6-(N-[5-Bromo-2-propoxybenzyl]-N-ethylamino)pyridazin-3-yl]tetrazole

6-[N-(5-Bromo-2-propoxybenzyl)-N-ethylamino]-3-cyanopyridazine (reference example 18) (1.0 g, 2.67 mmol), was dissolved in DMA (15 ml) and treated with sodium azide (520 mg, 8.0 mmol) followed by triethylammonium chloride (550 mg, 4.0 mmol) and the mixture heated at 110°C for 3 hours. The solution was poured 2M hydrochloric acid (50ml), extracted with ethyl acetate and dichloromethane (100ml of each) and the combined extracts washed with water (3x100ml), dried over $MgSO_4$ and concentrated in vacuo. Addition of ether and hexane precipitated a solid which was triturated with acetonitrile / toluene to give the title compound (965mg, 87%).

MS (ESP+): 418 $(M+H)^+$, 390 $(M+H-N_2)^+$

Elemental Analysis: $C_{17}H_{20}BrN_7O$

Calc: % C, 48.8; H, 4.82; N, 23.4

Found: % C, 49.1; H, 4.7; N, 23.5

NMR (250 MHz, DMSO-d_6) δ: 0.99 (t, J = 7Hz, 3H); 1.17 (t, J = 6 Hz, 3H); 1.72 (m, 2H); 3.72 (q, J = 6 Hz, 2H); 4.0 (t, J = 7Hz, 2H); 4.82 (s, 2H); 6.98 (d, J = 8.5 Hz, 1H); 7.22 (d, J = 2 Hz, 1H); 7.27 (d, J = 8 Hz, 1H); 7.40 (dd, J = 2, 8 Hz, 1H); 8.03 (d, J = 8.5 Hz, 1H).

Example 18

6-(N-[5-Bromo-2-propoxybenzyl]-N-ethylamino)pyridazine-3-carboxylic acid

6-[N-(5-Bromo-2-propoxybenzyl)-N-ethylamino]-3-cyanopyridazine (reference example 18) (1.5 g, 4 mmol) in ethanol (100 ml) was treated with aqueous sodium hydroxide (20ml, 2M, 40 mmol) and was heated to 70°C for 16 hours. The solvents were evaporated at reduced pressure, the residue dissolved in water, acidified with acetic acid and extracted with ethyl acetate (x4). The combined organic phases were washed with water and brine dried over $MgSO_4$ and concentrated in vacuo. The resulting gum was triturated with ether to give the title compound as solid (1.24 g, 79%).

M.p. 135-137°C

MS (ESP-): 392 (MH)$^-$,

Elemental Analysis: $C_{17}H_{20}BrN_7O$

Calc: % C. 51.8: H. 5.1; N. 10.7

Found: % C. 51.9; H. 5.3; N. 10.6

Example 19

N-Propyl-6-(N-[5-bromo-2-propoxybenzyl]-N-ethylamino)pyridazine-3-carboxamide

6-(N-[5-Bromo-2-propoxybenzyl]-N-ethylamino)pyridazine-3-carboxylic acid (example 18). (500 mg, 1.27 mmol) was dissolved in dichloromethane (50 ml), (1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDAC),(365mg, 2.07mmol), dimethylaminopyridine, (DMAP) (465 mg, 3.81 mmol) and propanesulfonamide (190 mg, 1.54 mmol) was added. The mixture was stirred at ambient temperature under argon overnight, after which TLC (5% methanol/dichloromethane) suggested the reaction was complete. The reaction mixture was loaded directly onto a MPLC column (silica) and the title compound obtained by elution 5% methanol / dichloromethane as a foam (380 mg, 60%).

MS(ESP+): 499 (M+H)$^+$

Elemental Analysis: $C_{20}H_{27}BrN_4O_4S$

Calc: % C, 48.1; H. 5.45; N, 11.2

Found: % C,48.2; H, 5.8; N, 10.8

NMR (250 MHz, DMSO-d_6) δ: 0.95 (m, 6H), 1.17 (t, J = 6 Hz, 3H); 1.7 (m, 2H); 3.37 (t, J = 8 Hz, 2H); 3.67 (q, J = 6 Hz, 2H); 3.95 (t, J = 6Hz, 2H); 4.82 (s, 2H); 6.98 (d, J = 8.5 Hz, 1H); 7.12 (d, J = 2 Hz, 1H); 7.17 (d, J = 8 Hz, 1H); 7.37 (dd, J = 2, 8 Hz, 1H); 7.83 (d, J = 8.5 Hz, 1H).

Example 20

N-(3,5-Dimethylisoxazo-4-ylsulphonyl)-6-(N-[5-bromo-2-propoxybenzyl]-N-ethylamino)pyridazine-3-carboxamide

6-(N-[5-Bromo-2-propoxybenzyl]-N-ethylamino)pyridazine-3-carboxylic acid (example 18) (500 mg, 1.27 mmol) was dissolved in dichloromethane (50 ml). (1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDAC),(365mg, 2.07mmol), dimethylaminopyridine. (DMAP) (465 mg. 3.81 mmol) and 3.5-dimethylisoxazoly-4-ylsulfonamide (270 mg, 1.53 mmol) was added. The mixture was stirred at ambient temperature under argon overnight, after which TLC (5% methanol/dichloromethane) suggested the reaction was complete. The reaction mixture was loaded directly onto a MPLC column (silica) and the title compound obtained by elution 5% methanol / dichloromethane as a gum which was further purified by trituration with ether to give the required product as a solid (180mg, 33%).

M.p. 122-124°C

MS(ESP+): 552 $(M+H)^+$

Elemental Analysis: $C_{22}H_{26}BrN_5O_5S \cdot 1.1\ H_2O$

Calc: % C, 47.8; H, 4.7; N, 12.7

Found: % C,46.2; H, 4.9; N, 12.2

NMR (250 MHz, DMSO-d_6) δ: 0.95 (m, J = 6 Hz ,3H), 1.12 (t, J = 7 Hz, 3H); 1.72 (m, 2H);); 2.27 (s, 3H);); 2.55 (s, 3H); 3.62 (q, J = 7 Hz, 2H); 3.95 (t, J = 6Hz, 2H); 4.72 (s, 2H); 6.93 (d, J = 8.5 Hz, 1H); 6.97 (d, J = 8 Hz, 1H); 7.17 (d, J = 2 Hz, 1H); 7.37 (dd, J = 2, 8 Hz, 1H); 7.77 (d, J = 8.5 Hz, 1H).

Example 21

6-[N-(5-Chloro-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]pyridazine-3-carboxamide

A mixture of N-ethyl-5-chloro-2-(cyclopropylmethoxy)benzylamine (reference example 20) (4.4g, 18.4mmol), 6-chloropyridazine-3-carboxamide (3.0g 19mmol), di-isopropylethylamine (5.0ml, 29mmol) and DMF (25ml) was stirred at reflux for 16 hours. The mixture was cooled and diluted with water (50ml), the gum was allowed to settle out and the supernatant liquor decanted. The gum was dissolved in dichloromethane and stirred while adding 2N hydrochloric acid (50ml). A precipitate formed after 10 minutes. The solid was filtered off and washed with dichloro methane (10ml) and ether (20ml) to give a buff solid (3.8g, 61%) m.p. 177-8°C

MS (ESP$^+$): 361/363 (M+H)$^+$)

NMR (200MHz. DMSO-d_6) δ 0.34 (m, 2H). 0.57 (m. 2H). 1.16 (t, J=7Hz. 3H). 1.25 (m. 1H). 3.70 (q, J=7Hz. 2H). 3.78 (d. 2H). 4.81 (s. 2H). 7.00 (d. J=8Hz. 1H). 7.05 (d. J=2Hz. 1H). 7.17 (d, J=9Hz. 1H). 7.25 (dd. J=2. 8Hz. 1H). 7.45 (broad s. 1H). 7.85 (d. J=9Hz. 1H). 8.07 (broad s. 1H).

Example 22

6-[N-(5-Chloro-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylic acid

The title compound was prepared as a white powder from 6-[N-(5-chloro-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]pyridazine-3-carboxamide (example 21) using a similar method to that of example 26.

(Yield 86%).

m.p. 119-120°C

MS (ESP$^+$) : 362/364 (M+H)$^+$

NMR (200 MHz, DMSO-d_6) δ 0.34 (m, 2H), 0.56 (m. 2H); 1.17 (t, J=7Hz. 3H), 1.22 (m, 1H), 3.72 (q, J=7Hz. 2H) 3.90 (d, J=7Hz. 2H), 4.83 (s. 2H), 7.02 (d, J = 8Hz.) 7.08 (d, J=2Hz. 1H), 7.14 (d, J=9Hz, 1H). 7.26 (dd. J=2, 8Hz. 1H), 7.84 (d, J = 9Hz. 1H).

Elemental Analysis:

Calculated % C, 59.8; H, 5.6; N, 11.6; Cl 9.8

Found % C, 59.7; H, 5.6; N, 11.7; Cl, 9.9

Example 23

5-[6-(N-[5-Chloro-2-cyclopropylmethoxybenzyl]-N-ethylamino)pyridazin-3-yl]tetrazole

The title compound was prepared from 6-[N-(5-chloro-2-cyclopropylmethoxybenzyl)-N-ethylamino]-3-cyanopyridazine (reference example 21) using a similar method to that of example 12.

(Yield 41%)

m.p. 190-192°C

MS (ESP$^+$): 386/388 (M+H)$^+$

NMR (200MHz. DMSO-d_6) δ 0.35 (m. 2H). 0.57 (m. 2H). 1.20 (t. J=7Hz. 3H). 3.77 (q. J=7Hz. 2H). 3.90 (d. J=7Hz. 2H), 4.85 (s. 2H). 7.01 (d. J=8Hz. 1H). 7.14 (d. J = 2Hz. 1H). 7.25 (dd. J=2.8 Hz. 1H). 7.29 (d. J = 8Hz. 1H). 8.04 (d. J=8Hz. 1H).

Analysis: Calc % C. 56.0; H. 5.2; N. 25.4

Found % C. 55.9; H. 5.3; N. 25.0

Example 24

N-Trifluoromethanesulphonyl-6-[N-(5-Chloro-2-cyclopropylmethoxybenzyl)-N-ethylamino]pyridazine-3-carboxamide

The title compound was prepared from 6-[N-(5-chloro-2-cyclopropylmethoxybenzyl)-N-ethylamino]pyridazine-3-carboxylic acid (example 22) and trifluoromethanesulphonamide using a similar method to that of example 7. (Yield 18%).

m.p. 150°-dec

MS (ESP^+): 493/495 $(M+H)^+$

NMR (200 MHz, DMSO-d_6) δ :0.35 (m, 2H), 0.57 (m. 2H). 1.15 (t, J=7Hz, 3H), 3.67 (q, J=7Hz, 2H), 3.88 (d, J=7Hz, 2H), 4.80 (s, 2H), 6.95 - 7.10 (m, 3H), 7.24 (dd, J=2, 8Hz, 1H), 7.80 (d, J=8Hz, 1H).

Example 25

6-[N-(5-Chloro-2-cyclopentoxybenzyl)-N-ethylamine]pyridazin-3-carboxamide

N-Ethyl-5-chloro-2-cyclopentoxybenzylamine (reference example 22 - used without further purification) (4.27 g, 16.8 mmol) in dimethylformamide (25 ml) was then treated with 6-chloropyridazin-3-carboxamide (described in reference example 3) (3.03 g, 19.2 mmol) and ethyl diisopropylamine (5 ml, 29 mmol) and left to reflux at 140 ^{0}C for 16 hours. Water (50 ml) was added and the product extracted into dichloromethane and ether, dried over anhydrous magnesium sulfate, filtered and purified by column chromatography (2% propan-2-ol in dichloromethane) to give 1.44 g of yellow gum. Trituration with ether yielded the title compound (790 mg, 13%).

MS (ESP+); 375 / 377 (MH+)

NMR (200 MHz. DMSO-d_6) δ: 1.08 (t, 3H): 1.60 (m. 6H); 1.87 (m, 2H); 3.62 (q, 2H); 4.74 (s. 2H); 4.85 (m. 1H): 7.03 (m. 2H); 7.13 (d. 1H); 7.24 (dd. 1H); 7.42 (br s. 1H); 7.82 (d, 1H); 8.08 (br s, 1 H).

Example 26

6-[N-(5-Chloro-2-cyclopentoxybenzyl)-N-ethylamine]pyridazin-3-carboxylic acid

6-[N-(5-Chloro-2-cyclopentoxybenzyl)-N-ethylamine]pyridazin-3-carboxamide (example 25) (0.75 g, 2.0 mmol) was dissolved in ethanol (50 ml), 2N sodium hydroxide (15 ml) added and the solution left to reflux at 80 ^{0}C for 16 hours. Once cool, the solvent was removed *in vacuo* and water (100 ml) added. The solution was acidified with glacial acetic acid and the title compound extracted into dichloromethane, washed with water (2 x 100 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the product recrystalised from dichloromethane, ether and hexane upon standing. (100 mg, 13%)

MS (ESP+): 376 / 378 (MH+)

NMR (200 MHz, DMSO-d_6, 373K) δ: 0.79 (t, 3H); 1.62 (m, 6H); 1.88 (m, 2H); 3.15 (m, 2H); 4.38 (s, 2H); 4.80 (m, 1H); 6.80 (br s, 1H); 6.95 (d, 1H); 7.22 (dd, 1H); 7.32 (d, 1H); 7.93 (d, 1H).

Example 27

5-[6-(N-[5-Chloro-2-cyclopentoxybenzyl]-N-ethylamino)pyridazin-3-yl]tetrazole

The title compound was prepared from 6-(N-[5-Chloro-2-cyclopentoxybenzyl]-N-ethylamino)-3-cyanopyridazine (reference example 23) using a similar method to that of example 12 except the reaction was stirred at 150 ^{0}C for 9 hours, the solution was acidified with 1N hydrochloric acid and the product was extracted into dichloromethane (2 x 100 ml) and purified by column chromatography (10% propan-2-ol, 0.1% methanoic acid in dichloromethane). Ether trituration gave the title product (225 mg, 18%).

MS (ESP+): 400 / 402 (MH+)

NMR (200 MHz. DMSO-d_6) δ: 1.14 (t, 3H); 1.60 (m. 4H); 1.70 (m. 2H); 1.88 (m. 2H); 3.65 (q, 2H); 4.78 (s. 2H); 4.87 (m. 1H); 7.02 (d. 1H), 7.13 (d. 1H); 7.28 (m. 2H); 8.03 (d. 1H).

Example 28

N-(3.5-Dimethylisoxazol-4-ylsulphonyl)-6-[N-(5-bromo-2-(2-methylpropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxamide.

The title compound was prepared from 6-[5-bromo-2-(2-methylpropoxy)benzyl)-N-ethylamino]pyridine-3-carboxylic acid (example 9) and 3.5-dimethylisoxazol-4-ylsulphonamide using a similar method to that of example 14.

NMR(200Hz. DMSO-d_6) δ 0.98 (d. 6H); 1.15(t. 3H); 1.95-2.06 (m. 1H); 2.38(s. 3H); 2.7 (s. 3H); 3. 69 (q. 2H); 3.8 (d. 2H); 4.85 (s. 2H); 6. 98 (d. 1H); 7.13 (d. 1H); 7.2 (d, 1H); 7.39 (dd. 1H); 7.8 (d. 1H).

Example 29

6-[N-(5-Methanesulphonyl-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylic acid.

6-(N-(5-Methanesulphonyl-2-(cyclopropyloxy)benzyl)-N-ethylamino]-3-cyanopyridazine (900mg, 2.3 mmol) in ethanol (30ml) and water (6ml) was treated with sodium hydroxide pellets (0.93g, 23 mmol) and the resultant solution heated at 80°C overnight (the reaction was monitored by HPLC). The mixture was then evaporated to low volume, water was added and the mixture extracted with ethyl acetate (x3) (a small quantity of insoluble material was ignored). The aqueous layer was acidified with acetic acid and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and evaporated to leave a gum. The gum was dissolved in dichloromethane and evaporated to give the title compound as a foam (0.56g, 60%) MS (ESP$^-$): 404 (M-H$^-$). NMR (200MHz, DMSO-d_6) δ 0.3-0.4 (m, 2H); 0.52 - 0.6 (m, 2H); 1.1-1.3 (m + t, 4H); 3.05 (s, 3H); 3.72 (q, 2H); 4.0 (d, 2H); 4.87 (s, 2H); 7.18 (d, 1H); 7.24 (d, 1H); 7.58 (d, 1H); 7.8 (dd, 1H); 7.84 (d, 1H).

Example 30

N-(Propanesulphonyl)-6-[N-(5-methanesulphonyl-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]pyridazine-3-carboxamide.

The title compound was prepared from 6-[N-(5-methanesulphonyl-2-(cyclopropylmethoxy)benzyl)N-ethylamino]pyridazine-3-carboxylic acid (example 29) using a similar method to that of example 14.

MS (ESP^+): 511.2 $(M+H)^+$.

NMR (200MHz, DMSO-d_6) δ: 0.29-0.38 (m. 2H): 0.5-0.62 (m. 2H); 0.98 (t. 3H); 1.3-1.1 (m + t. 4H); 1.65-1.82 (m. 2H): 3.05 (s. 3H): 3.43 (t. 2H); 3.75 (q. 2H): 4.0 (d. 2H); 4.9 (s, 2H): 7.23 (d. 1H); 7.27 (d. 1H): 7.56 (d. 1H): 7.8 (dd. 1H); 7.85(d. 1H).

Example 31

N-Propanesulphonyl-6-[N-(5-bromo-2-(2-methylpropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxamide.

The title compound was prepared from the corresponding acid (Example 9) using a method similar to that of Example 7.

NMR (250MHz DMSO-d_6) δ: 1.00 (m, 9H); 1.15 (t, 3H); 1.75 (m, 2H); 2.03 (m, 1H); 3.45(m. 2H); 3.70 (q, 2H); 3.80 (d. 2H); 4.86 (s, 2H); 7.0 (d, 1H), 7.13 (d, 1H); 7.21 (d, 1H); 7.40 (dd, 1H); 7.87 (d, 1H).

Example 32

N-(3,5-Dimethylisozazol-4-ylsulphonyl)-6-[N-(5-bromo-2-(3,3,3-trifluoro-2-hydroxypropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxamide.

The title compound was prepared from 6-[N-(5-bromo-2-(3,3,3-trifluoro-2-hydroxypropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylic acid (example 15) using a similar method to that of example 7.

NMR (250MHz ,DMSO-d_6) δ: 1.15(t, 3H); 2.35(s, 3H); 2.63 (s, 3H); 3.68 (q, 2H); 4.2 (m, 2H); 4.40(m, 1H); 4.82(s. 2H); 6.6: d, 1H); 7.05(m, 2H); 7.2(m. 1H); 7.40 (dd, 1H); 7.80 (d, 1H);

MS (ESP+) 622 $(M+H)^-$.

Example 33

6-[N-(5-Bromo-2-(cyclobutyloxy)benzyl)-N-ethylamino]pyridazine-3-carboxylic acid.

The title compound was prepared from the corresponding nitrile (reference example 24) using a similar method to that of example 29.

MS (ESP^+): 406 $(M+H)^+$.

NMR (250MHz DMSO-d_6) δ 1.15(t, 3H); 1.73 (m, 2H); 2.00 (m, 2H); 2.42(m, 2H); 3.69(q, 2H); 4.72 (quintet, 1H); 4.81 (s, 2H); 6.82 (d, 1H); 7.12 (d, 1H); 7.16 (d, 1H); 7.36 (dd, 1H); 7.83 (d, 1H).

Example 34

5-[6-(N-[5-bromo-2-(3,3,3-trifluoro-2-hydroxypropoxy)benzyl]-N-ethylamino)pyridazin-3-yl]tetrazole

The title compound was prepared from the corresponding nitrile (reference example 25) by a similar method to that of example 12.

MS $(ESP)^+$: 488 $(M+H)^+$.

NMR (250MHz DMSO-d_6) δ: 1.18(t,3H); 3.72(q,2H); 4.16 (m, 1H); 4.27 (m, 1H); 4.44 (m, 1H); 4.84 (s, 2H); 6.66 (bd, 1H); 7.08 (d, 1H); 7.19 (d, 1H); 7.25 (d, 1H); 7. 41 (dd, 1H); 8.03 (d, 1H).

Example 35

2-[N-(5-Bromo-2-cyclopropylmethoxybenzyl)-N-ethylamino]pyridine-5-carboxylic acid

2-[N-(5-Bromo-2-cyclopropylmethoxybenzyl)-N-ethylamino]-5-cyanopyridine (reference xample 26) (7.5g, 19.43mmol) was dissolved in ethanol (400ml) and sodium hydroxide (7.8g, 174mmol) and then water (80ml) added. The mixture was heated at reflux for 16 hours, the ethanol removed in vacuo, and the residue extracted with ethyl acetate (4x100ml). The organic extracts were acidified with acetic acid and washed with water (100ml) to give a solid (6.8g). This solid was dissolved in n-butanol (400ml) and sodium hydroxide (6.75g, 169mmol) and water (80ml) was added. The mixture was heated

at reflux for 72 hours. the butanol removed in vacuo. water (100ml) added and the residue extracted with ethyl acetate(4x100ml). The organic extracts were acidified with acetic acid and washed with water (100ml). The combined aqueous layers were then acidified and extracted with ethyl acetate (4x100ml) to give the title product as a solid (2.4g. 30%).
M.p.175-177°C

MS: 404 (M-H)$^-$
NMR (MHz, DMSO-d_6) δ: 0.30(m. 2H); 0.55 (m. 2H): 1.12(m. 4H); 3.55 (q. 2H): 3.85 (d, 2H); 4.68 (s. 2H): 6.62(d. 1H): 6.92 (d, 1H): 7.05 (d, 1H): 7.35 (dd. 1H); 7.88 (dd. 1H); 8.58 (d. 1H)12.30(s. 1H).

Elemental Analysis: $C_{19}H_{21}BrN_2O_3$
Calc: % C, 56.3; H, 5.2; N, 6.9
Found: % C. 56.1; H, 5.3; N, 6.8

Example 36

6-[N-(5-Chloro-2-cyclobutylmethoxybenzyl)-N-ethylamino]pyridazine-3-carboxylic acid

The title compound was prepared from using a similar method to that of example 18 by treating 6-[N-(5-Chloro-2-cyclobutylmethoxybenzyl)-N-ethylamino]-3-cyanopyridazine (reference example 27) (2.3g, 6.46mmol) with sodium hydroxide (2.6g, 65mmol) in water (20ml) and ethanol (100ml) to give a gum which solidified on trituration with ether (1.15g, 47%).
M.p.140-142°C

MS: 374 (M-H)$^-$
NMR (MHz, DMSO-d_6) δ: 1.1(t, 3H); 1.95 (m. 6H); 2.70(m, 1H); 3.68 (q, 2H); 4.0 (d, 2H); 4.8 (s, 2H); 7.0(m, 3H); 7.25(dd, 1H); 7.82 (d, 1H).
Elemental Analysis: $C_{19}H_{22}ClN_3O_3$
Calc: % C, 60.5; H, 5.9; N, 11.2
Found: % C. 60.5: H, 6.0; N. 10.9

Example 37

6-[N-(5-Bromo-2-cyclopropylmethoxybenzyl)-N-propylamine]pyridazine-3-carboxylic acid

The title compound was made from the corresponding ester [which was prepared using similar methods to those described in reference example 3, using propylamine in place of ethylamine, and reference example 4] using a similar method to that of example 1 (20%).

MS (ESP+) : 420 / 422 (MH+)

NMR (200 MHz, DMSO-d_6) δ: 0.25 (m, 2H); 0.57 (m, 2H); 0.91 (t, 3H); 1.21 (m, 1H); 1.61 (m, 2H); 3.63 (t, 2H); 3.88 (d, 2H); 4.83 (s, 2H); 6.96 (d, J=8Hz, 1H); 7.13 (d, J=9Hz, 1H), 7.16 (d, J=2Hz, 1H); 7.38 (dd, J=2Hz, 8Hz, 1H); 7.82 (d, J=9Hz, 1H).

Example 38

N-(3,5-Dimethylisoxazol-4-ylsulphonyl)-6-[N-(5-Bromo-2-cyclopropylmethoxybenzyl)-N-propylamine]pyridazine-3-carboxamide

The title compound was prepared from 6-[N-(5-Bromo-2-cyclopropylmethoxybenzyl)-N-ethylamine]pyridazine-3-carboxylic acid (example 37) using a similar method to that of example 7, except that dichloromethane was used as the solvent and no column purification was neccessary. Recrystalisation (diethyl ether/hexane) gave the title compound (340 mg, 49%).

MS (ESP+) : 578 / 580 (MH+)

NMR (250 MHz, DMSO-d_6) δ: 0.33 (m, 2H); 0.54 (m, 2H); 0.88 (t, 3H); 1.19 (m, 1H); 1.60 (m, 2H); 2.40 (s, 3H) 2.68 (s, 3H); 3.60 (t, 2H); 3.87 (d, 2H); 4.84 (s, 2H); 6.96 (d, J=8Hz, 1H); 7.17 (d, J=2 Hz, 1H); 7.23 (d, J=9 Hz, 1H); 7.38 (dd, J=2Hz,8Hz, 1H); 7.81 (d, J=9 Hz, 1H).

Example 39

6-[N-(5-Bromo-2-cyclopropylmethoxybenzyl)-N-methylamino]pyridazine-3-carboxylic acid

The title compound was prepared using a similar method to that of example 37 from the appropriate N-methyl compound.

MS (ESP+) : 392 / 394 (MH+)

NMR (250 MHz, DMSO-d_6) δ: 0.33 (m. 2H); 0.55 (m. 2H); 1.19 (m. 1H): 3.38 (d, 2H): 4.86 (s. 2H); 6.97 (d, J=8Hz. 1H); 7.17 (d. J=10 Hz. 1H); 7.20 (d. J=2Hz. 1H): 7.37 (dd. J=8Hz. 2Hz. 1H): 7.84 (d. J=10 Hz).

Example 40

N-(3,5-Dimethylisoxazol-4-ylsulphonyl)-6-[N-(5-bromo-2-cyclopropylmethoxybenzyl)-N-methylamino]pyridazine-3-carboxamide

The title compound was prepared using a similar method to that of example 38 from the corresponding carboxylic acid.

MS (ESP+) : 550 / 552 (MH+)

NMR (250 MHz, DMSO-d_6) δ: 0.30 (m. 2H); 0.52 (m. 2H): 1.16 (m. 1H): 2.39 (s. 3H); 2.69 (s. 3H): 3.22 (s. 3H): 3.85 (d, 2H): 5.87 (s. 2H): 6.95 (d, J=8Hz. 1H); 7.20 (d, J=2 Hz, 1H); 7.27 (d. 1H); 7.39 (dd. J=2Hz. 8Hz. 1H); 7.84 (d, 1H).

Reference Example 1

Methyl 2-[N-(5-bromo-2-propoxybenzyl)-N-ethylamino]pyridine-5-carboxylate

6-Chloronicotinic acid (100 g, 0.63 mol) was treated with ethylamine (70% in water. 500 ml). The reaction was sealed in an autoclave and heated to 170°C for 6 hours. The reaction mixture was evaporated, partially neutralised with concentrated HCl and the pH adjusted to pH5 with glacial acetic acid. The solid product was filtered off and dried in vacuo for 18 hours to give 6-(ethylamino)nicotinic acid (87.8 g, 84%).

MS (CI^+) = 167 $(M+H)^+$

NMR (250 MHz, DMSO-d_6) δ: 1.15 (t, J=7Hz, 3H); 3.3 (q, J=7Hz, 2H); 6.45 (d, J=9Hz, 1H); 7.25 (brt, 1H); 7.78 (dd, J=2, 9Hz, 1H); 8.54 (d, J=2Hz, 1H); 11.6 (brs, 1H).

A suspension of 6-(ethylamino)nicotinic acid (50 g, 0.3 mol) in methanol (500 ml) was treated with concentrated H_2SO_4 (30 ml). The reaction was heated at reflux for 18 hours. The reaction mixture was then evaporated, poured into ice water (1L) and adjusted to pH8 with solid sodium hydrogen carbonate (foaming). The aqueous mixture was extracted with

ethyl acetate (3 x 300 ml) and the organic layers combined, dried ($MgSO_4$) and evaporated to give methyl 6-(ethylamino)nicotinoate as an off-white solid (45.5 g, 84%).

NMR (200 MHz, DMSO-d_6) δ: 1.14 (t, J=7Hz, 3H); 3.3 (q, J=7Hz, 2H); 3.76 (s, 3H); 6.46 (d, J=9Hz, 1H); 7.39 (brt, 1H); 7.80 (dd, J=3, 9Hz, 1H); 8.56 (d, J=3Hz, 1H).

A solution of 5-bromosalicyladehyde (12.0 g, 59.7 mmol) in DMF (50 ml) was treated with K_2CO_3 (16.5 g, 120 mmol) and benzyl bromide (11.2 g, 65.6 mmol). The reaction was stirred at ambient temperature for 18 hours, diluted with ethyl acetate and filtered. The filtrate was washed with HCl (0.05 M), saturated aqueous sodium hydrogen carbonate and brine. The organic phase was dried (Na_2SO_4) and evaporated and the residue triturated with hexane/ethyl ether. The product was filtered off to give 2-benzyloxy-5-bromobenzaldehyde as a white solid (15.8 g, 90%) m.p. 70-72°C.

MS (CI+): 291 $(M+H)^+$

NMR (200 MHz, DMSO-d_6) δ: 5.38 (s, 2H); 7.5 (m, 6H); 7.9 (m, 2H); 10.41 (s, 1H).

A suspension of 2-benzyloxy-5-bromobenzaldehyde (14.5 g, 50.2 mmol) in absolute ethanol (250 ml) was treated with sodium borohydride (2.6 g, 68.8 mmol). The reaction was stirred and the temperature slowly rose to 33°C. After 1 hour the reaction mixture was evaporated and the residue dissolved in ethyl acetate and poured into a mixture of ice water (200 ml) and 1N HCl (25 ml). The organic layer was separated, washed with aqueous sodium hydrogen carbonate, brine, dried (Na_2SO_4) and evaporated to give 2-benzyloxy-5-bromobenzylalcohol as a pale yellow oil (14.85 g, quantitative).

MS (CI+) 292 (M+).

NMR (200 MHz, DMS0-d_6) δ: 4.52 (d, J=5Hz, 2H); 5.12 (s, 2H); 5.17 (t, J=5Hz, 1H); 6.98 (d, J=9Hz, 1H); 7.4 (m, 6H); 7.5 (d, 2H, 1H).

A solution of 2-benzyloxy-5-bromobenzyl alcohol (14.75 g, 50.2 mmol) in anhydrous ethyl ether (150 ml) was cooled to 4°C. A solution of PBr3 (13.68 g, 50 mmol) in anhydrous ether (40 ml) was added dropwise keeping the temperature below 10°C. The reaction was allowed to warm to ambient temparture and stirred for 1 hour. The reaction was filtered through silica gel (200 g). The silica gel was washed with ethyl ether to remove all the product. The filtrate was washed with water (1 x 150 ml), aqueous saturated sodium hydrogen carbonate (1 x 150 ml) and brine (1 x 150 ml). The organic layer was dried (Na_2SO_4) and evaporated to give 2-benzyloxy-5-bromobenzylbromide as a pale yellow oil (15.2 g, 85%) which crystallised on standing.

MS (EI+): 354 (M+)
NMR (200 MHz, DMSO-d_6): δ 8:4.65 (s. 2H); 5.2 (s. 2H); 7.05 (d, J=9Hz, 1H), 7.4 (m, 6H); 7.66 (d, J=3Hz. 1H).

A solution of methyl 6-ethylaminonicotinoate (15.2 g, 84.4 mmol) in DMF (50 ml) was cooled to 0°C and treated with sodium hydride (60%, 75 mmol). The reaction was stirred for 1 hour and a solution of 2-benzyloxy-5-bromobenzylbromide (25 g, 70.2 mmol) in DMF (50 ml) added. The reaction was allowed to warm to ambient temperature and stirred for 18 hours. The reaction was quenched with water and extracted with ethyl acetate (three times). The organic layers were combined, washed with water and brine twice, dried ($MgSO_4$) and evaporated to give a white solid. Recrystallisation from ethyl acetate/hexane gave methyl 2-[N-(2-benzyloxy-5-bromobenzyl)-N-ethylamino]pyridine-5-carboxylate (22.7 g, 71%).

MS (CI+): 455/457 $(M+H)^+$

NMR (200 MHz, DMSO-d_6) δ: 1.1 (t, J=7Hz, 3H); 3.5 (q, J=7Hz, 2H); 3.78 (s, 3H); 4.77 (s, 2H); 5.18 (s, 2H); 6.65 (d, J=9Hz, 1H); 7.08 (m, 2H); 7.4 (m, 6H); 7.9 (dd, J=2, 9Hz, 1H); 8.62 (d, 1H).

A solution of methyl 2-[N-(2-benzyloxy-5-bromobenzyl)-N-ethylamino]pyridine-5-carboxylate (10.0 g. 22 mmol) in dichloromethane (950 ml) was treated with boron trichloride dimethyl sulphide complex (40 ml. 2M. 80 mmol). The reaction was stirred at ambient temperature for 48 hours. Saturated aqueous sodium hydrogen carbonate solution was added and the layers were washed with dichloromethane. The organic layers were combined. dried ($MgSO_4$) and evaporated to give an off white solid which was subjected to chromatography (eluant: ethyl acetate/hexane) to give methyl 2-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]pyridine-5-carboxylate (6.02 g. 75%).

MS (CI^+): 365 $(M+H)^+$

NMR (250MHz. DMSO-d_6): δ 1.14 (t. J=7Hz. 3H): 3.61 (q, J=7Hz, 2H); 3.78 (s. 3H); 4.66 (s. 2H); 6.65 (d, J=9Hz, 1H): 6.8 (d. J=9Hz. 1H); 7.02 (d, J=2Hz, 1H); 7.2 (dd. J=2, 9Hz, 1H); 7.93 (dd, J=2. 9Hz, 1H); 8.64 (d, J=2Hz. 1H): 10.13 (s. 1H).

1-Bromopropane (0.12 g, 0.69 mmol) was treated with a solution of methyl 2-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]-5-pyridylcarboxylate (0.2 g, 0.55 mmol) in DMF (4 ml). Potassium carbonate (230 mg, 1.7 mmol) was added to this solution and the reaction mixture was stirred for 18 hours. The solvent was evaporated and the residue taken up in water (4 ml) and extracted with ethyl acetate (3 x 3 ml). The combined extracts were evaporated and the residue subjected to chromatography (eluant: ethyl acetate/hexane) to give the title compound as a pale yellow oil (0.122 g, 54%) which was used in the subsequent step without further purification.

Reference Example 2

Methyl 2-[N-(5-bromo-2-(2-methylpropoxy)benzyl)-N-ethylamino]-pyridine-5-carboxylate

A solution of the methyl-2-[N-(5-bromo-2-(hydroxy-benzyl)-N-ethylamino]pyridine-5-carboxylate (reference example 1, paragraph 7) (0.5 g, 1.37 mmol) in THF (15 ml) was treated with triphenylphosphine (0.39 g, 1.49 mmol) and diazoethyldicarboxylate. The reaction was stirred at ambient temperature for five minutes

and then isobutyl alcohol (0.152. 2.06 mmol) added. The reaction was then stirred at ambient temperature for 18 hours. partitioned between ethyl acetate and water and the aqueous layer washed with ethyl acetate (x2). The organic layers were combined, washed with water and brine. dried ($MgSO_4$) and evaporated. The residue was subjected to chromatography (eluant: ethyl acetate/hexane) to give the title compound (0.35 g, 60%) as an off-white solid.

MS (CI^+): 421 $(M+H)^+$

NMR (250 MHz, DMSO-d_6) δ: 1.0 (d, J=6Hz. 3H); 1.12 (t, J=7Hz. 6H); 2.04 (m, 1H); 3.6 (q, J=7Hz. 2H); 3.78 (s, 3H); 3.80 (s, 2H); 4.75 (s, 2H); 6.66 (d, J=9Hz. 1H); 6.97 (d, J=9Hz. 1H); 7.05 (d. J=2Hz. 1H); 7.37 (dd, J=2, 9Hz, 1H); 7.93 (dd, J=2. 9Hz. 1H); 8.73 (d, J=2Hz, 1H).

Reference Example 3

Butyl 6-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]-pyridazine-3-carboxylate

A solution of 6-oxo-1,6-dihydropyridazine-3-carboxylic acid (British patent no. 856409) (52 g, 0.33 mol) in nBuOAc (80 ml) and butanol (80 ml) was treated with concentrated sulphuric acid (5 ml). The mixture was heated at reflux under a Dean-Stark trap. After 5 hours water production had ceased. The reaction was allowed to cool to ambient temperature and after standing overnight, the precipitate was filtered, washed with diethyl ether and dried to give butyl 6-oxo-1,6-dihydropyridazine-3-carboxylate as a white solid (55.2 g, 85%) m.p. 81-83°C.

A solution of the above butyl ester (55.2 g, 0.28 mol) in acetonitrile (220 ml) was added carefully to $POCl_3$ (55.2 ml, 0.60 mol). The resultant solution was stirred at 100°C for 2 hours. The reaction was cooled, evaporated at reduced pressure. The residue was dissolved in dichloromethane (280 ml) and added to a cold stirred solution of sodium carbonate (55 g) in water (280 ml). The mixture was stirred until all effervescence ceased, then the layers were separated and the organic layers dried ($MgSO_4$) and filtered through a pad of silica gel. The solution was evaporated to give butyl 6-chloropyridazine-3-carboxylate as a pale pink solid (51 g, 85%).

A solution of the chloro pyridazine compound from the previous step (51 g, 0.238 mole) in THF (375 ml) was treated with methanolic ammonia (saturated. 80 ml). The reaction was allowed to stand at ambient temperature overnight. The precipitate was filtered and dried to give 6-chloropyridazine-3-carboxamide as a pink solid (18.2 g, 49%). [Further material could be obtained by evaporating the filtrate (at reduced pressure) and treating the residue with THF (100 ml) and methanolic ammonia (40 ml). The product was isolated as before to give a pink solid (17.4 g). Total yield (35.6 g, 95%)].

A suspension of 6-chloropyridazine-3-carboxamide (28.5 g, 0.18 mol) in methanol (200 ml) was treated with aqueous ethylamine (70% solution. 77 ml). The reaction was heated at reflux for 3½ hours. The reaction was allowed to cool to ambient temperature and stand overnight. The precipitate was filtered and washed with a small volume of water and dried to give 6-(ethylamino)pyridazine-3-carboxamide as pink solid (8.9 g). [The filtrates were evaporated to a small volume diluted with cold water (100 ml) and more of the desired solid was filtered-off, washed with water and dried (12.8 g). Total yield (21.7 g, 72%)].

A solution of 6-(ethylamino)pyridazine-3-carboxamide (21.7 g, 0.131 mol) in n-butanol (109 ml) and $BF_3.Et_2O$ (54 ml) was heated under an air condenser (allowing evaporation of Et_2O) at 120°C for 18 hours. The reaction was evaporated at reduced pressure and the residue dissolved in ice/water (400 ml) and neutralized with stirring using solid sodium bicarbonate. The oily precipitate was extracted with dichloromethane (250 ml) containing methanol (50 ml). The extracts were dried ($MgSO_4$) and evaporated (in vacuo) to give a slightly sticky solid which was recrystallized from ethyl acetate (~250 ml) to give butyl 6-(ethylamino)pyridazine-3-carboxylate as an off-white solid (22.0 g, 75%).

A suspension of the butyl ester from the previous step (21 g, 0.094 mol) in acetic acid (400 ml) was treated with 4-bromophenol (65.5 g, 0.378 mol) and paraformaldehyde (3.15 g, 0.105 mol). The reaction was heated at 100°C for 4.5 hours and a further portion of paraformaldehyde (6.3 g, 0.21 mol) added and the reaction heated at 100°C for 16 hours. The resulting dark coloured reaction was evaporated to give a dark oil. Chromatography (eluant: diethyl ether/hexane) gave fast running materials as a brown oil. This oil was dissolved in ethyl acetate (~ 70 ml) and allowed to stand overnight at ambient

temperature to give a white solid precipitate. which was filtered and washed with ethyl acetate and dried to give butyl 6-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]pyridazine-3- carboxylate as the product (12.3 g, 32%).

<u>Reference Example 4</u>

<u>Butyl 6-[N-(5-bromo-2-cyclopropylmethoxybenzyl)-N-ethylamino]pyridazine-3-carboxylate</u>

A solution of n-butyl 6-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]pyridazine-3- carboxylate (reference example 3) (0.286 g, 0.69 mmol) in DMF (3.5 ml) was treated with bromomethylcyclopropane (0.1 g, 0.78 mmol) and potassium carbonate (0.473 g. 3.4 mmol). The reaction was allowed to stir at ambient temperature for 60 hours. The solvent was evaporated at reduced pressure (vacuum pump) and the residue partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (2 x 10 ml). The organic layers were combined dried ($MgSO_4$) and evaporated. The residue was purified by chromatography (eluant : ethyl acetate/hexane) to give the title compound as a pale yellow oil (0.3 g, 94%).

MS (ESP+): 462 $(M+H)^+$

NMR (200 MHz, DMSO-d_6) δ: 0.32 (m, 2H); 0.55 (m, 2H); 0.93 (t, J = 7Hz. 3H); 1.15 (m, 4H); 1.42 (m, 2H); 1.7 (m, 2H); 3.7 (q, J = 7Hz, 2H); 3.89 (d, J = 7Hz, 2H); 4.3 (t, J = 7H, 2H); 4.84 (s, 2H); 6.98 (d, J = 8Hz, 1H); 7.15 (m, 2H); 7.4 (dd, J = 3.9Hz); 7.82 (d, J = 8Hz. 1H).

<u>Reference Example 5</u>

<u>Methyl 2-[N-(5-bromo-2-(cyclopentylmethoxy)benzyl)-N-ethylamino]pyridine-5-carboxylate</u>

The title compound was prepared using a similar method to that of reference example 2 (from the phenol in reference example 1, paragraph 7) using cyclopentylmethanol in place of isobutyl alcohol to give a yield of 60%.

MS (ESP+): $(M+H)^+$ 447

NMR (200 MHz. DMSO-d_6) δ: 1.11 (t. J = 7Hz. 3H): 1.35 (m. 2H): 1.58 (m. 4H): 1.77 (m. 2H): 2.3 (m. 1H): 3.6 (q. J = 7Hz. 2H): 3.79 (s. 3H): 3.9 (d. J = 7Hz. 2H): 4.75 (s. 2H): 6.68 (d. J = 9Hz. 1H): 6.8 (d. J = 9Hz. 1H): 7.07 (d. J = 2Hz. 1H): 7.38 (dd. J = 2. 9Hz. 1H): 7.94 (dd. J = 2. 9Hz. 1H): 8.65 (d. J = 2H. 1H).

Reference Example 6

Butyl 6-[N-(5-bromo-2-propoxybenzyl)-N-ethylamino]pyridazine-3-carboxylate

The title compound was prepared by reacting 1-iodopropane and butyl 6-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]pyridazine-3-carboxylate (reference example 3) using a similar method to that of reference example 4.

MS (ESP^+): 450/452 ($M+H^+$)

Reference Example 7

Butyl 6-[N-(5-bromo-2-butoxybenzyl)-N-ethylamino]pyridazine-3-carboxylate

The title compound was prepared by reacting 1-iodobutane and butyl 6-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]pyridazine-3-carboxylate using a similar method to that of reference example 4.

MS (ESP^+): 464/466 $(M+H)^+$

Reference Example 8

6-[N-(5-Bromo-2-hydroxybenzyl)-N-ethylamino]pyridazine-3-carboxylic acid

A solution of butyl 6-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]pyridazine-3- carboxylate (reference example 3) (0.36 g, 1.0 mmol) in THF (4 ml) and methanol (4 ml) was treated with aqueous sodium hydroxide 1N (4 ml) and allowed to stand at ambient temperature for 1.5 hours. The reaction was evaporated to a small volume, diluted with water and acidified with acetic acid. After standi for 18 hours, the precipitate was

filtered. washed with water and ether, and dried ($MgSO_4$) to give the title compound as a white solid (0.26 g, 71%).

MS : (ESP+) 352/354 $(M+H)^+$

NMR (200 MHz. DMSO-d_6) δ : 1.15 (t. J = 6.67Hz. 3H): 3.68 (q, J = 6.67Hz. 2H); 4.75 (s. 2H): 6.83 (d. J = 8.34Hz. 1H); 7.10 (d. J = 8.34Hz. 1H); 7.13(d, J = 2.33Hz. 1H): 7.25 (dd. J = 10.00, 2.33Hz. 1H); 7.83 (d. J = 10.00Hz. 1H).

Reference Example 9

2-[N-(5-Bromo-2-hydroxybenzyl)-N-ethylamino]pyridine-5-carboxylic acid

A solution of methyl 2-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]pyridine-5-carboxylate (see reference example 1) (10.2 g, 0.55 mmol) in THF (3 ml) and methanol (5 ml) was treated with 1N aqueous sodium hydroxide solution (2.7 ml) and was heated to 40°C for 24 hours. The solvents were evaporated at reduced pressure, the residue treated with 1N acetic acid (2.7 ml) and the precipitate filtered, washed with water and air dried to give the title compound (0.17 g, 92%).

MS (FAB+): 351 $(M+H)^+$

NMR (200 MHz. DMSO-d_6) δ: 1.12 (t, J = 7Hz. 3H); 3.6 (q, J = 7Hz. 2H); 4.64 (s, 2H); 6.6 (d, J = 9Hz, 1H); 6.83 (d, J = 9Hz, 1H); 7.06 (d, J = 2Hz, 1H); 7.23 (dd, J = 2, 9Hz, 1H); 7.92 (dd, J = 2, 9Hz, 1H); 8.59 (d, J = 2Hz, 1H).

Reference Example 10

Butyl 6-[N-(5-bromo-2-(2-methylpropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylate

Butyl 6-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]pyridine-3-carboxylate (reference example 3) (1.12g, 2.76mmol) in dimethylformamide (16ml) was treated with potassium carbonate followed by 1-bromo-2-methylpropane (0.16ml, 770mg, 5.6mmol) and stirred at ambient temperature overnight. TLC showed reaction to be incomplete so further potassium carbonate (1.12g) and 1-bromo-2-methylpropane were added and the

mixture stirred at ambient temperature over two days. The mixture was then evaporated to low bulk and the residue purified directly by MPLC to give the title compound as a colourless gum

(1.26g, 98%).

NMR (250 MHz, DMSO d_6) δ 0.90 (m, 9H); 1.15 (t, 3H); 1.42 (m, 2H); 1.70 (m, 2H); 2.03 (m, 1H); 3.73 (q 2H); 3.80 (d, 1H); 4.28 (t, 2H), 4.82 (s, 2H); 6.97 (d, 1H), 7.1 (m, 2H); 7.38 (dd, 1H); 7.81 (d, 1H).

Reference Example 11

Butyl 6-[N-(5-chloro-2-hydroxybenzyl)-N-ethylamino]pyridazine-3-carboxylate

The title compound was prepared from butyl 6-(ethylamino)pyridazine-3-carboxylate and 4-chlorophenol using a similar method to that of reference example 3, except 0.4 equivalents of trifluoroacetic acid were added to the reaction mixture.

NMR (250 MHz, DMSO-d_6) δ: 0.94 (t, 3H); 1.17 (t, 3H); 1.43 (m, 2H); 1.70 (m, 2H); 3.7 (q, 2H); 4.28 (t, 2H); 4.75 (s, 2H); 6.85 (d, 1H); 6.97 (d, 1H); 7.1 (m, 2H); 7.82 (d, 1H); 10.1 (bs, 1H).

Reference Example 12

Butyl 6-[N-(5-chloro-2-(2-methylpropoxy)benzyl)-N-ethyl]pyridazine-3-carboxylate

The title compound was prepared by reacting butyl 6-[N-(5-chloro-2-hydroxybenzyl)-N-ethylamino]pyridazine-3-carboxylate (reference example 11) with 1-bromo-2-methylpropane using a similar method to that of reference example 4.

NMR (200MHz, DMSO-d_6) δ: 0.95 (m, 9H); 1.15 (t, 3H); 1.43 (m, 2H); 1.70 (m, 2H); 2.03 (m, 1H); 3.68 (q, 2H); 3.80 (d, 2H); 4.28 (t, 2H); 4.83 (s, 2H); 6.99 (d, 1H); 7.04 (d, 1H); 7.10 (d, 1H); 7.26 (dd, 1H); 7.83 (d, 1H).

MS (ES^+): 420 $(M+H)^+$

Reference Example 13

N-Ethyl-5-bromo-2-(cyclopropylmethoxy)benzylamine

1-Methyl-2-pyrrolidinone (90ml) (NMP) was added to anhydrous potassium carbonate (27.6g, 0.2 mol) under argon. To the stirred mixture was added in portions 5-bromosalicylaldehyde (20.1 ml, 0.1mol) and the mixture stirred for 10 minutes. Bromomethylcyclopropane (14.4ml, 0.15mol) was dissolved in NMP (10ml) and added dropwise over 15 minutes below 30°C. The reaction temperature was increased to 35-40°C

for 3 hours, 70°C for 1 hour and then cooled to 35°C. Ethylamine hydrochloride (13.85g, 0.17 mol) was dissolved in methanol (60ml), and added quickly to the mixture which was then heated at 35-40°C for 3 hours and stirred overnight (allowing it to cool to ambient temperature). The reaction mixture was then cooled in ice. Sodium borohydride (5.3g, 0.14 mol) was dissolved in NMP (58ml) and added dropwise [effervescence and exotherm to 15°C] and the mixture heated to 40-45°C for 2 hours. The reaction mixture was then cooled in ice. 2N Hydrochloric acid (250mls) was added dropwise keeping the temperature below 30°C. The mixture was transferred to a separating funnel and extracted with ethyl acetate (x2). The combined organic layers were washed with 20% brine/water (x3) and brine (x1), dried over Na_2SO_4, filtered and evaporated. The residue was dissolved in ethyl acetate (100ml) and cooled in ice. Hydrogen chloride gas was then bubbled through the stirred solution. The title compound as the hydrochloride salt precipitated and was filtered off, washed with ethyl acetate (x2) and dried under high vacuum (12.6g, 28.5%).

NMR (200MHz, DMSO-d_6) δ : 0.37 (m, 2H); 0.58 (m, 2H); 1.27 (m, 4H); 2.95 (q, 2H); 3.89 (d, 2H); 4.07 (s, 2H); 7.02 (d, J=8.0Hz, 1H); 7.53 (dd, J = 8.0, 2.9Hz, 1H); 7.73 (d, J = 2.9Hz, 1H); 9.25 (br s, 2H).

MS (ESP$^+$): 284 $(M+H)^+$.

Reference Example 14

6-[N-(5-Bromo-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]-3-cyanopyridazine

6-[N-(5-Bromo-2-cyclopropylmethoxy)benzyl)-N-ethylamino]pyridazine-3-carboxamide (example 11) (2.03g) was suspended in pyridine (25ml) and cooled under argon to 4°C. Methanesulphonyl chloride (4.6ml, 59.5mmol) was added dropwise (exotherm to -8°C) followed by pyridine (20mls). The reaction mixture was allowed to warm and stirred overnight. The pyridine was removed under reduced pressure and the residue partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with 50% 1N HCl/saturated aqueous ammonium chloride (xl), saturated aqueous sodium bicarbonate (x1) and brine (x1), dried over Na_2SO_4, filtered and evaporated . The residue was purified by column chromatography, eluting with 2.5% ethyl

acetate/dichloromethane and the fractions containing the title product were evaporated to a gum. (1.65g, 85.0%).

NMR (200MHz, DMSO-d_6) δ 0.30 (m,2H): 0.54 (m,2H): 1.15(m,4H); 3.69(q,2H); 3.85(d,2H); 4.80(s,2H); 6.95(d,1H); 7.20(m,2H); 7.38(dd,1H); 7.80(d,1H).

MS(ESP$^-$): 386.8(M-H)$^-$.

Reference Example 15

6-[N-(5-Chloro-2-(2-methylpropoxy)benzyl)-N-ethylamino]-3-cyanopyridazine

6-[N-(5-Chloro-2-(2-methylpropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylic acid (example 10) (2.0g) was dissolved in pyridine (30ml) under argon and cooled to 4°C. Methanesulphonyl chloride (0.75ml, 9.7mmol) was added to the mixture which was stirred at 4°C for 1.5 hours to give a dark purple solution. Ammonia gas was then bubbled through the solution for 2 minutes to give a dark red solution (exotherm to +15°C) and the solution evaporated under reduced pressure. The residue was dissolved in pyridine (30ml) and cooled under argon to 4°C. Methanesulphonyl chloride (5.1ml, 66 mmol) was then added dropwise (exotherm to 10°C) and the resultant brown suspension stirred at ambient temperature overnight. The brown solution was then evaporated and the residue partitioned between saturated aqueous ammonium chloride and ethyl acetate. The organic layer was washed with 10% 2N HCl/saturated aqueous ammonium chloride (x2), saturated aqueous sodium bicarbonate (x1) and brine (x1), dried over Na_2SO_4, filtered and evaporated. The title product was isolated by column chromatography using 20% ethyl acetate/isohexane as eluant (1.18g, 62.2%). [OPPI 14 : 396-9 (1982)].

NMR(200MHz, DMSO-d_6) δ: 0.97(d,6H); 1.12(t,3H); 2.00(m,1H); 3.67(q,2H); 3.79(d,2H); 4.85(s,2H); 7.05(m,2H); 7.19(d,1H); 7.29(dd,1H); 7.84(d,1H).

MS(ES$^+$): 345 (M+H)$^+$.

Reference Example 16

n-Butyl 6-[N-(5-bromo-2-(2-hydroxy-3,3,3-trifluoropropoxy)benzyl)-N-ethylamino]pyridazine-3-carboxylate.

The title compound was prepared by reacting 3-bromo-1.1.1-trifluoropropan-2-ol and butyl 6-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]pyridazine-3-carboxylate using a similar method to that of reference example 4

NMR: (250MHz. DMSO-d_6) δ: 0.95(t,3H); 1.15(t.3H); 1.42(m.2H); 1.68(m.2H); 3.7(q.2H); 4.20(m,4H); 4.42(m,1H); 4.83(s.2H); 6.65(d,1H); 7.1(m,3H); 7.42(dd.1H); 7.63(d.1H).

Reference Example 17

6-[N-(2-(Cyclopropylmethoxy)-5-methanesulphonylbenzyl)-N-ethylamino]-3-cyanopyridazine

4-Methyl mercaptophenol (8.96g, 64 mmol) suspended in toluene (80ml) was added to magnesium methoxide solution in methanol (5.5ml, 8% soln, 41.4mmol) and the reaction stirred at reflux for 1 hour. After this time the yellow solution was treated with toluene (80ml) and methanol distilled from the reaction until reaction temperature reached approximately 95°C. Some solid precipitated. Paraformaldehyde (5.84g, 194 mmol) in toluene (60ml) was added to the mixture. which was stirred at reflux for 3.5 hours under argon (the temperature must be at least 95°C). The reaction mixture containing a little solid was then cooled and treated with 2N sulphuric acid (80ml), toluene (80ml), stirred for 15 minutes and separated. The organic layer was washed with water (x3). dried and evaporated to leave an orange oil (9.6g). This oil was purified by MPLC using 5% ether/isohexane to give 2-hydroxy-5-methylthiobenzaldehyde (3.3g).

NMR (200MHz, DMSO-d_6) δ: 2.45(s,3H); 6.98(d,J=9Hz,1H); 7.48(dd, J=2.3, 9.0Hz, 1H); 7.55(d,J=2.3Hz, 1H); 10.25(s,1H); 10.67(s,1H).

MS (CI+): 168(M^+).

2-Hydroxy-5-methylthiobenzaldehyde was alkylated with bromomethylcyclopropane using a similar method to that of reference example 4 to give 2-cyclopropylmethoxy-5-methylthiobenzaldehyde.

NMR(200MHz. DMSO-d_6) δ: 0.36(m.2H); 0.6(m.2H): 1.26(m,1H): 2.46(s,3H); 4.0(d.J=8.25Hz.2H); 7.2(d.J=9.2Hz. 1H); 7.52-7.62(m.2H); 10.38(s,1H):

MS (CI^+): $(M+H)^+$ 223.3.

N-Ethyl 2-cyclopropylmethoxy-5-methylthiobenzylamine was prepared by reductive amination of 2-cyclopropylmethoxy-5-methylthiobenzylamine using a similar method to that of reference example 19(1).

NMR(200MHz. DMSO-d_6) δ: 0.32(m.2H): 0.55(m,2H); 1.03(t,J=7.3Hz. 3H); 1.30-1.13(m,1H): 2.4(s,3H); 2.53(q, J = 7.3Hz, 2H); 3.65(s.2H); 3.82(d,J =6.25Hz. 2H); 6.88(d, J=8.3Hz, 1H); 7.10(dd. J= 2.5. 8.3Hz. 1H); 7.25(d, J= 2.5Hz. 1H).

MS (ESP^+): 252.4$(M+H)^+$.

N-Ethyl 2-cyclopropylmethoxy-5-methylthiobenzylamine was reacted with 3-chloro-6-cyanopyridazine (prepared in reference example 18) using a similar method to that of example 11 to give 6-[N-(2-cyclopropylmethoxy)-5-methylthiobenzyl)-N-ethylamino]-3-cyanopyridazine.

NMR(200MHz, DMSO-d_6) δ: 0.28(m,2H); 0.52(m,2H); 1.20-1.08(m,4H): 2.35(s,3H); 3.70(q,2H); 3.84(d, J=8.3Hz,2H); 4.8(s,2H); 6.95(d, J=8.3Hz,1H); 7.03(d, J=2.1Hz,1H); 7.19(dd, J=10.4, 2.1Hz, 2H); 7.8(d, J=10.4Hz, 1H).

MS (ESP+): 355$(M+H)^+$.

6-[N-(2-Cyclopropylmethoxy-5-methylthiobenzyl)-N-ethylamino]-3-cyanopyridazine (201mg, 0.57mmol) in dichloromethane (5ml) was cooled on ice to approximately -10°C and treated with 50% m-chloroperbenzoic acid (196mg, 0.57 mmol). The reaction mixture was stirred at -10 to 0°C for 1 hour, then diluted with dichloromethane and extracted with saturated aqueous sodium bicarbonate solution (x2). The organic extracts were dried and evaporated to give a pale brown foam (180mg). The foam (180mg, 0.49mmol) in dichloromethane (5ml) was cooled to -10°C, treated with m-chloroperbenzoic acid (170mg, 0.49 mmol) and stirred for 1.25 hours as the temperature rose to 0°C. More dichloromethane was added and the mixture extracted with saturated

aqueous sodium bicarbonate solution (x2). dried and evaporated to give a foam which was purified by MPLC using 2:1 ethyl acetate/hexane as eluant to yield the title product (100mg. 53%).

NMR (200MHz. DMSO-d_6) δ: 0.32(m.2H); 0.54(m.2H); 1.27-1.08(m.4H); 3.08(s.3H); 3.7(q.2H); 3.98(d. J=8.3Hz.2H); 4.88(s.2H); 7.22(d. J= 10.4 Hz,1H); 7.26(d. J = 10.4,Hz, 1H); 7.61(d, J = 2.1Hz, 1H); 7.77-7.78(m, J= 10.21Hz, 2H);

MS(ESP^+) $(M+H)^+$ 387.2.

<u>Reference Example 18</u>

<u>6-[N-(5-Bromo-2-propoxybenzyl)-N-ethylamino]-3-cyanopyridazine</u>

(1) A mixture of 6-chloropyridazine-3-carboxamide (described in reference example 3) (15g, 95.5mmol) and pyridine (22.6g, 23.1ml, 286.6mmol) were was suspended in dichloromethane and cooled to -30°C under argon. TFAA was added dropwise to the stirred mixture keeping the internal temperature below -20°C . The reaction was stirred for 19.5hours allowing to warm to ambient temperature. The mixture was poured into water(500ml) and washed with water (4x500ml) until the aqueous phase was pale yellow. The organic phase was dried over $MgSO_4$, filtered through a pad of silica (50mm diameter, 30mm deep), and concentrated in vacuo. The resulting solid was purified by MPLC (40% dichloromethane/20%ethyl acetate/hexane) to give 3-chloro-6-cyanopyridazine as a colourless solid (5.25g, 59%).

MS (EI+): 139 (M^+)

NMR (250 MHz, $CDCl_3$) δ: 7.71 (d, J=8Hz, 1H); 7.83 (d, J=8Hz, 1H).

(2) A solution of 5-bromosalicyladehyde (20 g, 100 mmol) in NMP (100 ml) was treated with K_2CO_3 (41.4 g, 300 mmol) at 40°C for 30 minutes. n-Propyl iodide (25.5g, 150mmol) was added and the reaction mixture stirred at 40°C for 19hours. A solution of ethylamine hydrochloride (11.41g, 140mmol) in ethanol (50ml) was added and the mixture stirred at 40°C for a further 3hours, after which a solution of sodium borohydride (5.292g, 140mmol) in NMP (20ml) was added dropwise over 1hour (CAUTION: much foaming). The reaction was stirred at 40°C for 19 hours cooled to ambient temperature and 5M

hydrochloric acid (500ml). The solution was then treated with 5M sodium hydroxide solution to pH 14 and extracted with ethyl acetate (3x300ml). The combined organic phases were washed with water (4x500ml) dried over potassium carbonate and dry HCl gas was passed over the solution. The slurry was concentrated in vacuo to give a yellow solid which was recrystallised from acetonitrile / toluene to give N-ethyl 2-propoxy-5-bromobenzylamine hydrochloride as a white solid.
(15.47g, 50%).

MS (ESP): 375 (MH^-)
NMR (250 MHz, $CDCl_3$) δ: 1.02 (t, J=7Hz, 3H); 1.25 (t, J=6Hz, 3H); 1.80 (m, 2H); 3.77 (q, J=6Hz, 2H); 3.92 (t, J=7Hz, 2H); 4.80 (brs, 2H); 6.67 (d, J=8.5Hz, 1H); 6.75 (d, J=Hz, 1H); 7.12 (d, J=2Hz, 1H); 7.34 (dd, J=8, 2Hz, 1H); 7.38 (d, J=8.5Hz, 1H).

(3) N-ethyl 2-propoxy-5-bromobenzylamine hydrochloride 2 (5.17g, 16.8mmol) and 3-chloro-6-cyanopyridazine (2.65g, 16.8mmol) were dissolved in NMP (25ml) and sodium hydrogen carbonate added (3.54g, 42.1mmol). The mixture was heated at 110°C under argon afor 7.5hours and then allowed to cool to ambient temperature. The mixture was poured into ethyl acetate (200ml) washed with water (5x200ml) and brine (200ml), the organic phase dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by MPLC (20%ethyl acetate / hexane) and then crystallised from ether / hexane to give the title product (4.80g, 76%).

MS (ESP): 272 (MH^+), 227 $(M-EtNH_2)^+$
NMR (250 MHz, DMSO-d_6) δ: 0.99 (t, J=6Hz, 3H); 1.26 (t, J=7Hz, 3H); 1.78 (m, 2H); 2.92 (q, J=7Hz, 2H); 3.95 (t, J=6Hz, 2H); 4.02 (s, 2H); 7.02 (d, J=8Hz, 1H); 7.52 (dd, J=8, 2Hz, 1H); 7.75 (d, J=2Hz, 1H); 9.32 (brs, 2H).

Reference Example 19

6-[N-(5-Bromo-2-hydroxybenzyl)-N-ethylamino]-3-cyanopyridazine

(1) A solution of 5-bromo salicylaldehyde (20.1g 0.1mmol) in THF (150ml) was treated with a solution of ethylamine in methanol (2M. 70ml. 0.14 mmol). The reaction was stirred at ambient temperature for 1.5 hours. After cooling in an ice bath. sodium borohydride (5.3g, 0.14 mmol) was added portionwise. The reaction was allowed to stand at ambient temperature overnight. Water was added and the solvent removed at reduced pressure. The residue was dissolved in ethyl acetate and washed with water and the organic layer dried over MgSO4 and acidified with gaseous HCl. N-Ethyl-5-bromo-2-hydroxybenzylamine hydrochloride was collected by filtration as a white solid. (17.53g, 66%).

NMR (250MHz, DMSO-d_6) δ: 1.23(t,3H); 2.94(q,2H); 4.60(t,2H); 6.96(d,1H); 7.37(dd,1H); 7.63(d,1H); 9.02(bs,1H); 10.59(s,1H).

MS(ESP$^+$): 230/232 $(M+H)^+$.

(2) The title compound was prepared by reacting N-ethyl-5-bromo-2-hydroxybenzylamine hydrochloride and 3-chloro-6-cyanopyridazine using a similar method to that of reference example 18 except eluting with 2% diethyl ether/dichloromethane in the chromatography (yield 50%).

NMR (250MHz, DMSO-d_6) δ 1.15(t,3H); 8.37(q,2H); 4.75(s,2H); 6.81(d,1H); 7.07(d,1H); 7.15(d,1H); 7.25(dd,1H); 7.82(d,1H); 10.12(bs,1H).

Reference Example 20

N-Ethyl-5-chloro-2-(cyclopropylmethoxy)benzylamine.

The title compound was prepared by reacting 5-chloro-2-hydroxybenzaldehyde with bromomethylcyclopropane using a similar method to reference example 4.

MS (CI$^+$): 240/242 $(M+H)^+$.

NMR (200MHz, $CDCl_3$) δ0.34(m,2H); 0.63(m,2H); 1.13(t, J = 7Hz, 23H); 1.26(m,1H); 2.65(q, J = 7Hz, 2H); 3.78(d,2H); 3.80(d,2H); 6.72(d, J = 8Hz, 1H); 7.13(dd, J = 2, 8Hz, 1H); 7.21(d, J = 2Hz, 1H).

Reference Example 21

6-[N-(5-Chloro-2-(cyclopropylmethoxy)benzyl)-N-ethylamino]-3-cyanopyridazine

To a stirred mixture of 6-[N-(5-chloro-2-(cyclopropylmethoxy)benzyl)-N-ethylamine]pyridazine-3-carboxamide (3.5g, 9.7mmol in pyridine (120ml) at 20°C, was added dropwise during 20 minutes, methane sulphonyl chloride (10.0ml, 124 mmol). The mixture was stirred at 20°C for 60 hours and poured onto ice (300gm) and 10N hydrochloric acid (100ml), stirring vigorously, then extracted with ether (500ml). The organic layer was washed with 1N hydrochloric acid (500ml), dried over anhydrous magnesium sulphate and evaporated to give the title product as a light brown gum, (3.3g, 99%).

MS (ESP^+): 343/345 $(M+H)^+$.

NMR (200 MHz, $CDCl_3$) δ 0.32(m,2H); 0.60(m,2H), 1.20(m,1H); 1.25(t, J = 7Hz, 3H); 3.82 (d,2H); 3.85(q, J = 7Hz, 2H); 4.85(s, 2H); 6.78(d, J = 8Hz, 1H); 7.06(d, J = 8Hz, 1H); 7.09(d, J = 2Hz, 1H); 7.22(dd, J = 2, 8Hz, 1H); 7.52(d, J = 8Hz, 1H).

Reference Example 22

N-Ethyl 5-chloro-2-(cyclopentoxy)benzylamine

To 5-chlorosalicyaldehyde (20.3 g, 130 mmol) and bromocyclopentane (22.0 g, 148 mmol) in dimethylformamide (100 ml) was added anhydrous potassium carbonate (23.4 g, 169 mmol) and the solution stirred at 50 °C for 16 hours. The inorganic solid was extracted and the solvent removed *in vacuo*. The product was extracted into dichloromethane from water (200 ml) and the organic layer subsequently dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The redissolved product

was purified by flushing through a silica plug (dichloromethane) and washing with 2 normal sodium hydroxide solution (100 ml x 3) to yield 5-chloro-2-cyclopentoxybenzaldehyde
(19.22 g, 66%).

M.S. (CI+): 225 / 227 (MH+)
NMR. (200 MHz. DMSO-d_6) d : 1.80 (m. 8H): 4.98 (m,1H); 7.24 (d, J=8 Hz, 1H); 7.58 (d, J=2Hz, 1H); 7.62 (dd. J=2.8 Hz, 1H); 10.28 (s, 1H).

5-Chloro-2-cyclopentoxybenzaldehyde (9.35 g, 41.6 mmol) and ethylamine hydrochloride (18.6 g, 229 mmol) in methanol (100 ml) for 30 minutes at ambient temperatures, following which sodium cyanoborohydride (5.6 g, 88 mmol) was added and the reaction left to reflux at 70 ^{0}C for 70 hours with periodic acidification to pH 6 using glacial acetic acid. Normal hydrochloric acid (100 ml) was added in a dropwise fashion and the resultant mixture basified with 2 normal sodium hydroxide solution until a pH of 11 existed, whereupon the product was extracted into dichloromethane (250 ml x 2) and ethyl acetate (250 ml x 2). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed to yield the title compound (8.5 g, 80%).

Reference Example 23

6-(N-[5-Chloro-2-(cyclopentoxy)benzyl]-N-ethylamino)-3-cyanopyridazine

The title compound was prepared by reacting reference example 22 and 3-chloro-6-cyanopyridazine (reference example 18(1)) using a similar method to that of reference example 18(3).

Reference Example 24

6-[N-(5-Bromo-2-(cyclobutyloxy)benzyl)-N-ethylamino]-3-cyanopyridazine

The title compound was prepared by alkylation of the appropriate nitrile (reference example 18) with bromocyclobutane using a similar method to that of reference example 4. except that the reaction was stirred at ambient temperature for 10 days.

MS (ESP)$^+$: 387 (M+H)$^+$.

NMR (250MHz. DMSO-d_6) δ: 1.14(t, 3H): 1.73 (m. 2H); 1.98(m. 2H): 2.40(m. 2H); 3.68 (q. 2H): 4.72 (quintet. 1H): 4.81 (s. 2H): 6.82(d. 1H): 7.2(m. 2H); 7.37 (dd, 1H); 7.83(d. 1H).

Reference Example 25

6-[N-(5-Bromo-2-(3,3,3-trifluoro-2-hydroxypropoxy)benzyl)-N-ethylamino]-3-cyanopyridazine.

The title compound was prepared by reacting 6-[N-(5-bromo-2-hydroxybenzyl)-N-ethylamino]-3-cyanopyridazine with 1,1,1-trifluoro-3-bromo-propan-2-ol using a method similar to that of reference example 4.

M.S. (ESP)+: 445 (M+H)$^+$.

NMR: (250MHz, DMSO-d_6) δ: 1.15 (t, 3H); 3.68(q, 2H); 4.16 (m, 1H); 4.25 (m, 1H); 4.4(m. 1H); 4.85(s. 2H); 6.65(d. 1H); 7.14(m. 3H); 7.43(dd, 1H); 7.83 (d, 1H).

Reference Example 26

2-[N-(5-Bromo-2-cyclopropylmethoxybenzyl)-N-ethylamino]-5-cyanopyridine

The title compound was prepared by reacting N-ethyl-5-bromo-2-cyclopropylmethoxybenzylamine (reference example 13) and 2-chloro- 5-cyanopyridine using a similar method to that of reference example 18.

MS: 386 (M+H)$^+$

NMR (MHz. DMSO-d_6) δ: 0.33 (m. 2H): 0.55 (m, 2H): 1.15 (m, 4H): 3.60 (q. 2H); 3.88 (d, 2H); 4.75 (s, 2H): 6.70(d. 1H); 6.95 (d. 1H); 7.05 (d, 1H); 7.35 (dd. 1H); 7.75 (dd, 1H); 8.45 (d. 1H).

Reference Example 27

6-[N-(5-Chloro-2-cyclobutylmethoxybenzyl)-N-ethylamino]-3-cyanopyridazine

Cyclobutanemethanol(5g. 58 mmol) was dissolved in dichloromethane (150ml) and cooled in an ice water bath. Triethylamine (10.5ml. 75.5mmol)was added followed by the dropwise addition of a solution of tosyl chloride (13.3g, 69.8mmol) in dichloromethane (50ml). The cooling bath was removed and the mixture allowed to cwarm to room temperature over 16 hours. The mixture was washed with water (2x100ml), dried ($MgSO_4$) and concentrated in vacuo to give cyclobutanemethanol tosylate as a yellow oil which was used without further purification.

MS: 241 $(M+H)^+$

5-Chlorosalicylaldehyde (7.7g, 49.4 mmol) was dissolved in DMF (20ml) with potassium carbonte (7.5g, 54.1mmol) and the cyclobutanemethanol tosylate (13g, 54.1mmol). The mixture was stirred at 50°C under argon for 16 hours. Poured into water (500ml), extracted with ethyl acetate (4x100ml)and the combined organic fractions washed with 1M sodium hydroxide solution (100ml) , water (100ml), saturated brine (100ml) dried ($MgSO_4$) and concentrated in vacuo to give 5-chloro-2-(cyclobutylmethoxy)benzaldehyde as a brown oil (13g) which was used without further purification.

MS: 225 $(M+H)^+$

5-hloro-2-(cyclobutylmethoxy)benzaldehyde (13g) was dissolved in DMF (100ml) and potassium carbonate (16g, 116 mmol) added followed by ethylamine hydrochloride (9.5g, 117mmol) . The mixture was heated at 40°C for 1 hour then cooled in an ice water bath and a solution of sodium borohydride (4.3g, 116mmol) in minimal DMF added dropwise. When addition was complete the cooling bath was removed and the reaction mixture heated to 40°C for 16 hours. The reaction was cooled to room temperature and 5M hydrochloric acid added cautiously wtil the mixture was at pH 2. Solid sodium hydroxide was then added to adjust the pH to 14 and the mixture was extracted with ethyl acetate (3x300ml) the combined organic fractions washed with water (100ml), saturated brine

(100ml) dried ($MgSO_4$) and concentrated in vacuo to give an oil (15g). This oil purified by MPLC (5% methanol / dichloromethane) to give N-ethyl 5-chloro-2-(cyclobutylmethoxy)benzylamine as a gum which crystallised on standing (2.1g, 17%).

MS: 254 $(M+H)^+$

NMR (MHz, DMSO-d_6) δ: 1.05(t, 3H); 1.95 (m, 6H); 2.50(m, 1H); 2.75 (q, 2H); 3.65 (s, 2H); 3.92 (d, 2H); 6.95(d, 1H); 7.20 (dd, 1H); 7.28 (d, 1H).

N-Ethyl 5-chloro-2-(cyclobutylmethoxy)benzylamine (2.1g, 8.3mmol) was coupled to the 3-chloro-5-cyanopyridazine (1.3g, 8.25mmol) with sodium hydrogen carbonate (0.71g, 8.45mmol) in NMP (10ml) in a similar method to that of reference example 18. The title compound was purified by MPLC(dichloromethane, 1%MeOH/dichloromethane) (2.3g, 78%) to give a solid.

MS: 357 $(M+H)^+$

NMR (MHz, DMSO-d_6) δ: 1.1(t, 3H); 1.95 (m, 6H); 2.60(m, 1H); 3.65 (q, 2H); 3.95 (d, 2H); 4.8 (s, 2H); 6.95(d, 1H); 7.00 (d, 1H); 7.18 (d, 1H); 7.26(dd, 1H); 7.82 (d, 1H).

Reference Example 28

N-Ethyl-5-bromo-2-(cyclopropylmethoxy)benzylamine

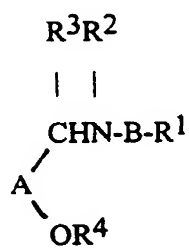
To 5-bromosalicylaldehyde (15.0 g, 74 mmol) in dimethylformamide was added anhydrous potassium carbonate (36.8 g, 266 mmol) and bromomethylcyclopropane (9 ml, 93 mmol) and the solution stirred at 50 ^{0}C for 60 hours. Propylamine (26.5 g, 450 mmol) was then added and the solution left to stir at ambient temperatures for 2 hours, afterwhich diethyl ether (50 ml) and sodium borohydride (2.6 g, 68 mmol) were added and the solution left for another hour. 6 Normal hydrochloric acid (150 ml) was then added dropwise and the solution left to stir for 16 hours. Impurities were extracted with diethyl ether (200 ml x 2), the solution basified with caustic liquor and the product then extracted into diethl ether (250 ml). The organic layer was then dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to give the title compound (4.8 g, 22%).

MS (EI+) : 298 / 300 (MH+)

NMR (200 MHz. DMSO-d_6) δ : 0.34 (m.2H); 0.56 (m.2H): 0.88 (t, 3H); 1.22 (m, 1H); 1.44 (m. 2H); 2.47 (t. 2H); 3.66 (s, 2H): 3.82 (d. 2H); 6.86 (d. J=8 Hz, 1H); 7.31 (dd. J=2Hz. 8Hz. 1H); 7.46 (d. J2 Hz. 1H).

CLAIMS

1. A compound of the formula I:



(I)

wherein:

A is an optionally substituted:

phenyl, naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidyl, thienyl, thiazolyl, oxazolyl or thiadiazolyl having at least two adjacent ring carbon atoms:

provided that the $-CH(R^3)N(R^2)B-R^1$ and $-OR^4$ groups are positioned in a 1.2 relationship to one another on ring carbon atoms and the ring atom positioned ortho to the OR^4 linking group (and therefore in the 3-position relative to the $-CHR^3NR^2-$ linking group) is not substituted;

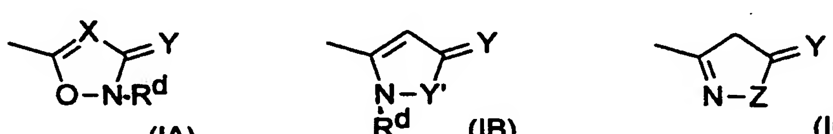
B is an optionally substituted:

phenyl, pyridyl, thiazolyl, oxazolyl, thienyl, thiadiazolyl, imidazolyl, pyrazinyl, pyridazinyl or pyrimidyl;

R^1 is positioned on ring B in a 1.3 or 1.4 relationship with the $-CH(R^3)N(R^2)-$ linking group and is carboxy, carboxyC_{1-3}alkyl, tetrazolyl, tetrazolylC_{1-3}alkyl, tetronic acid, hydroxamic acid, sulphonic acid, or R^1 is of the formula $-CONR^aR^{a1}$ wherein R^a is hydrogen or C_{1-6}alkyl and R^{a1} is hydrogen, C_{1-6}alkyl (optionally substituted by halo, amino, C_{1-4}alkylamino, di-C_{1-4} alkylamino, hydroxy, nitro, cyano, trifluoromethyl, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl), C_{2-6}alkenyl (provided the double bond in not in the 1-position), C_{2-6}alkynyl (provided the triple bond is not in the 1-position), carboxyphenyl, 5- or 6-membered heterocyclylC_{1-3}alkyl, 5- or 6-membered heteroarylC_{1-3}alkyl, 5- or 6-membered heterocyclyl, or 5- or 6-membered heteroaryl or R^a and R^{a1} together with the amide nitrogen to which they are attached (NR^aR^{a1}) form an amino acid residue or ester thereof, or R^1 is of the formula $-CONHSO_2R^b$ wherein R^b is C_{1-6}alkyl (optionally

substituted by halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-4}alkoxy, amino, C_{1-4}alkylamino, di-C_{1-4}alkylamino or C_{1-4}alkoxycarbonyl), C_{2-6}alkenyl (provided the double bond is not in the 1-position), C_{2-6}alkynyl (provided the triple bond is not in the 1-position), 5- or 6-membered heterocyclylC_{1-3}alkyl, 5- or 6-membered heteroarylC_{1-3}alkyl, phenylC_{1-3}alkyl, 5- or 6-membered heterocyclyl, 5- or 6-membered heteroaryl or phenyl;

wherein any heterocyclyl or heteroaryl group in R^{a1} is optionally substituted by halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl and any phenyl, heterocyclyl or heteroaryl group in R^b is optionally substituted by halo, trifluoromethyl, nitro, hydroxy, amino, cyano, C_{1-6}alkoxy, C_{1-6}alkylS(O)p-(p is 0, 1 or 2), C_{1-6}alkyl carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoylamino, C_{1-4}alkanoyl(N-C_{1-4}alkyl)amino, C_{1-4}alkanesulphonamido, benzenesulphonamido, aminosulphonyl, C_{1-4}alkylaminosulphonyl, di(C_{1-4}alkyl)aminosulphonyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkanoyloxy, C_{1-6}alkanoyl, formylC_{1-4}alkyl, hydroxyiminoC_{1-6}alkyl, C_{1-4}alkoxyiminoC_{1-6}alkyl or C_{1-6}alkylcarbamoylamino; or R^1 is of the formula -SO2N(R^c)R^{c1} wherein R^c is hydrogen or C_{1-4}alkyl and R^{c1} is hydrogen or C_{1-4}alkyl; or R^1 is of the formula (IA), (IB) or (IC):



(IA) (IB) (IC)

wherein X is CH or nitrogen, Y is oxygen or sulphur, Y' is oxygen or NR^d and Z is CH_2, NR^d or oxygen provided that there is no more than one ring oxygen and there are at least two ring heteroatoms and wherein R^d is hydrogen or C_{1-4}alkyl;

R^2 is hydrogen, C_{1-6}alkyl, optionally substituted by hydroxy, cyano or trifluoromethyl, C_{2-6}alkenyl (provided the double bond is not in the 1-position), C_{2-6}alkynyl (provided the triple bond is not in the 1-position), phenylC_{1-3}alkyl or pyridylC_{1-3}alkyl;

R^3 is hydrogen, methyl or ethyl;

R^4 is optionally substituted: C_{1-6}alkyl, C_{3-7}cycloalkylC_{1-3}alkyl or C_{3-7}cycloalkyl; or an N-oxide of $-NR^2$ where chemically possible;
or an S-oxide of sulphur containing rings where chemically possible:
or a pharmaceutically acceptable salt or in vivo hydrolysable ester or amide thereof: excluding 2-[2-methoxybenzylamino]pyridine-5-carboxylic acid, 4-[2-methoxybenzylamino]benzoic acid, 5-[2,3-dimethoxybenzylamino]-2-chloro-3-aminosulphonylbenzoic acid and 5-[2,5-dimethoxybenzylamino]-2-hydroxybenzoic acid.

2. A compound according to claim 1 wherein A is optionally substituted phenyl.

3. A compound according to either claim 1 or claim 2 wherein R^3 is hydrogen.

4. A compound according to any one of claims 1 to 3 wherein R^2 is hydrogen, methyl, ethyl or propyl.

5. A compound according to any one of claims 1 to 4 wherein B is optionally substituted: pyridyl, phenyl, thiazolyl, thienyl, pyridazinyl, or oxazolyl.

6. A compound according to any one of claims 1 to 5 wherein R^1 is carboxy, carbamoyl or tetrazolyl or R^1 is of the formula $-CONR^aR^{a1}$ wherein R^a is hydrogen or C_{1-6}alkyl and R^{a1} is C_{1-6}alkyl optionally substituted by hydroxy, C_{2-6}alkenyl, 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl, pyridylC_{1-3}alkyl or R^1 is of the formula $-CONHSO_2R^b$ wherein R^b is optionally substituted: C_{1-6}alkyl, phenyl or 5- or 6-membered heteroaryl.

7. A compound according to any one of claims 1 to 5 wherein R^1 is carboxy, tetrazole or of the formula $-CONHR^{a1}$ wherein R^{a1} is pyridylmethyl or C_{1-4}alkyl optionally substituted by hydroxy, or of the formula $-CONHSO_2R^b$ wherein R^b is C_{1-4}alkyl, 3,5-dimethylisoxazol-4-yl or 5-acetamido-1,3,4-thiadiazol-2-yl.

8. A compound according to any one of claims 1 to 7 wherein A is substituted by halo, nitro, trifluoromethyl, cyano, amino, C_{1-6}alkoxy, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, C_{1-4}alkanoylamino, C_{1-6}alkyl$S(O)_p$, C_{1-4}alkanesulphonamido, benzenesulphonamido, C_{1-6}alkanoyl, C_{1-4}alkoxyiminoC_{1-4}alkyl or hydroxyiminoC_{1-4}alkyl.

9. A compound according to any one of claims 1 to 8 wherein B is substituted by halo, trifluoromethyl, C_{1-4}alkyl, amino, C_{1-4}alkylamino, di-C_{1-4}alkylamino, nitro, hydroxy, C_{1-6}alkoxy or cyano or B is unsubstituted (other than as depicted in the formula (I)).

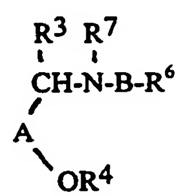
10. A compound according to any one of claims 1 to 9 wherein R^4 is optionally substituted C_{1-4}alkyl, C_{3-6}cycloalkyl or C_{3-6}cycloalkylmethyl.

11. A compound according to claim 1 which is any one of examples 1 to 40 or a pharmaceutically-acceptable salt thereof.

12. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 11 and a pharmaceutically acceptable carrier.

13. A method [illegible]g pain by administering an effective amount of a compound of the for[illegible] patient in need thereof.

14. A process for preparing a compound according to claim 1 which comprises deprotecting a compound of the formula (III):



(III)

wherein R^6 is R^1 as defined in claim 1 or protected R^1, R^7 is R^2 as defined in claim 1 or protected R^2 and, R^3, R^4, A and B are as defined in claim 1, and any optional substituents are optionally protected and at least one protecting group is present;

and thereafter if necessary:

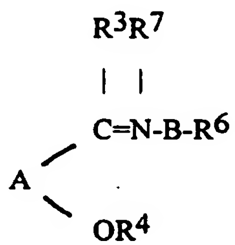
i) forming a pharmaceutically acceptable salt;

ii) forming an *in vivo* hydrolysable ester or amide;

iii) converting one optional substituent into another optional substituent.

15. A process for preparing a compound according to claim 1 or a compound of the formula (III) as defined in claim 14 which comprises:

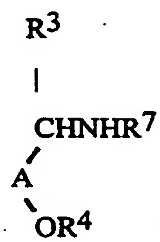
a) reducing a compound of the formula (IV)



(IV)

or

b) when B is an activated heterocycle and R^7 is hydrogen or C_{1-6}alkyl reacting a compound of the formula (V) with a compound of the formula (VI):



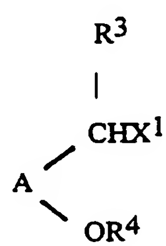
(V)

$X\text{-}B\text{-}R^6$ (VI)

or

c) reacting a compound of the formula (VII) with a compound of the formula (VIII):

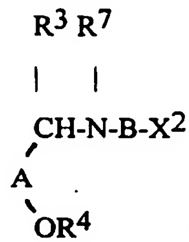
$R^7HN\text{-}B\text{-}R^6$ (VII)



(VIII)

or

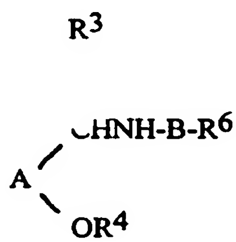
d) converting X^2 to R^6 in a compound of the formula (IX):



(IX)

or

e) when R^7 is other than hydrogen, reacting a compound of the formula R^7X^3 with a compound of the formula (X):



(X)

or

f) reacting a compound of the formula (XI) with a comound of the formula (XII):

R^3
|
CH-OH
/
A
\
OR^4 (XI)

$X^4NH\text{-}B\text{-}R^6$ (XII)

or

g) reacting a compound of the formula (XIII) with a compound of the formula (XIV):

R^3
|
CH-X^5
/
A
\
OR^4 (XIII)

$X^6NH\text{-}B\text{-}R^6$ (XIV)

or

h) reacting a compound of the formula (XV) with a compound of the formula X^7R^4:

R^3R^7
| |
CHN-B-R^6
/
A
\
OH (XV)

wherein R^3, R^4, R^7, R^9, A and B are as defined in claim 14 and X and X^1 are leaving groups, X^2 is a precursor of R^7, X^3 is a leaving group, X^4 is a removable activating group, X^5 is a leaving group, X^6 is an activating group and X^7 is a leaving group; and thereafter if necessary;

i) removing any protecting groups;

ii) forming a pharmaceutically acceptable salt;

iii) forming an in vivo hydrolysable ester or amide;

iv) converting an optional substituent into another optional substituent.

16. A compound of the formula (III) as defined in claim 14.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/01442

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/80 C07D237/24 C07D403/04 C07D401/04 C07D417/12
A61K31/455 A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 135 087 (WELLCOME) 27 March 1985 see page 15; claims; example 2 ---	1,12
A	EP,A,0 475 206 (ABBOTT) 18 March 1992 see claims ---	1,12
A	CHEMICAL ABSTRACTS, vol. 91, no. 27, 1979 Columbus, Ohio, US; abstract no. 56831t, page 691; XP002012511 see abstract	1,12
A	& JP,A,07 941 881 (BEECHAM) 3 April 1979 ---	1,12
P,X	WO,A,96 03380 (ZENECA) 8 February 1996 see the whole document -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 1996	10.09.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB96/01442

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1, 14-16
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
please see enclosed form!

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Meaningful Search Not Possible Or Incomplete Search
2. Lack Of Conciseness
Please see Article 6 PCT: The definition of the symbols of formula (I) and (III) is very general and encompasses such a big amount of products, that a complete search is not possible on economic grounds (PCT SEARCH GUIDELINES CHAPTER III, 3.6). The search has been limited to the following cases:
A = phenyl, naphtyl group
B = phenyl, pyridil or pyridoziryl group

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 96/01442

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-135087	27-03-85	DE-A-	3472252	28-07-88
		JP-C-	1730346	29-01-93
		JP-B-	4017190	25-03-92
		JP-A-	60056957	02-04-85
		US-A-	4590199	20-05-86
EP-A-475206	18-03-92	AU-B-	647174	17-03-94
		AU-B-	8374491	12-03-92
		CA-A-	2050723	11-03-92
		JP-A-	7053551	28-02-95
		JP-A-	4261156	17-09-92
		US-A-	5210206	11-05-93
		US-A-	5250548	05-10-93
		US-A-	5284954	08-02-94
WO-A-9603380	08-02-96	AU-B-	2988395	22-02-96